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New Developments in Biotechnology

4 U.S. Investment in Biotechnology

CONGRESS OF THE UNITED STATES
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Foreword

Since the discovery of recombinant DNA in the early 1970s, biotechnology has become an essential tool for many industries. The potential of biotechnology to improve the Nation's health, food supply, and the quality of the environment leads logically to questions of whether current levels of investment in research and development, human resources, and policy formulation are adequate to meet these expectations.

This special report is the fourth in a series of OTA studies being carried out under an assessment of "New Developments in Biotechnology," requested by the House Committee on Energy and Commerce and the House Committee on Science, Space, and Technology. This fourth report in the series describes the levels and types of investment currently being made by the Federal, State, and private sectors. Ten major issues that affect investment were identified. They concern levels of R&D funding, research priorities, interagency coordination, information requirements, training and education needs, monitoring of university-industry research, State efforts to promote biotechnology, the effects of tax law on commercial biotechnology, the adequacy of Federal assistance for biotechnology start-ups, and the effects of export control on biotechnology commerce. The first publication in the series was *Ownership of Human Tissues and Cells*, the second was *Public Perceptions of Biotechnology*, and the third was *Field-Testing Engineered Organisms*. A subsequent study will examine issues relevant to patenting plants, animals, and micro-organisms.

OTA was assisted in preparing this study by a panel of advisors, four workshop groups, and reviewers selected for their expertise and diverse points of view on the issues covered in the report. OTA gratefully acknowledges the contribution of each of these individuals. As with all OTA reports, responsibility for the content of the special report is OTA's alone. The special report does not necessarily constitute the consensus or endorsement of the advisory panel, the workshop groups, or the Technology Assessment Board.

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*Resigned February 1988.

NOTE: OTA is grateful for the valuable assistance and thoughtful critiques provided by the Advisory Panel members. The views expressed in this OTA report, however, are the sole responsibility of the Office of Technology Assessment.

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

SUMMARY

Biotechnology can change the way we live. It has already provided, and promises to provide, many products never before available, as well as greater quantities of products now in short supply. Some products produced by biotechnology will be less expensive and safer to use than those now produced by other means. The potential of biotechnology to improve the Nation's health, food supply, and the quality of the environment leads logically to questions about the adequacy of current funding levels.

This report, the fourth in a series on new developments in biotechnology, analyzes the current level of support for biotechnology by the Federal Government, by State and local governments, and by the private sector. The report is titled "U.S. Investment in Biotechnology;" investment indicates expectation that the expenditures will result in significant benefits to society. Investment is treated broadly in this report to encompass financial resources, human resources, and industrial policies.

Any analysis, however, is confounded by wide variation in the definitions used by various sectors to describe biotechnology, and in the methods used to account for that investment. As a consequence, figures on expenditures are approximate, and the scope of investment cannot be determined precisely. It is important to look beyond the numbers to the scale and diversity of efforts underway within the United States to support research in biotechnology and its various applications. In this report, **biotechnology is broadly defined to include any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific use. This report focuses on "new biotechnology" (e.g., recombinant DNA techniques, cell fusion, and novel bioprocessing techniques) rather than "old biotechnology" (e.g., use of micro-organisms for brewing and baking or selective breeding in agriculture and animal husbandry).**

Several conclusions are apparent about the nature of U.S. investment in biotechnology.

First, in some areas, the investment level is insufficient to meet the promise suggested by current work in the area. In particular, progress in such areas as agricultural biotechnology and biological approaches to waste disposal is hindered by inadequate investment by the public and private sectors. In both fields, technical barriers exist because of incomplete knowledge of basic processes involving plants, micro-organisms, and microbial ecology.

Second, the regulatory process is often perceived to be a significant obstacle to commercial development of some biotechnology-related products. Whether the perceptions are due to ambiguity, unresponsiveness, extreme caution, or outright bias, confusing regulatory mechanisms are seen by industry officials as a major impediment to the acquisition of knowledge and an obstacle to the economic success of future products. On the other hand, industry officials agree that reasonable and well designed regulations are necessary to ensure the public health and safety to the environment.

Third, the rate of biotechnology commercialization and the factors affecting that rate vary among industrial sectors. Policy issues relevant to the application of biotechnology to human therapeutics, for example, differ from those relevant to plant agriculture or chemicals.

How Much Does the United States Spend on Biotechnology?

Twelve Federal agencies and one cross agency program spent roughly $2.7 billion in fiscal year 1987 to support research and development in biotechnology-related areas (see table 1-1). The National Institutes of Health (NIH) contribute by far the largest share of that support, approximately $2.3 billion. Significant investment

Table 1-1.—Federal Support for Biotechnology Research, 1985-87 (current dollars in thousands)

Agency	FY 1985	FY 1986	FY 1987
National Institutes of Health:			
Basic	1,208,229	1,202,094	1,388,337
Applied	638,916	678,003	887,614
Total	1,847,145	1,880,097	2,275,951
Department of Defense:			
Basic	44,100	51,600	60,800
Applied	48,500	49,000	58,000
Total	92,600	100,600	118,800
National Science Foundation	81,570	84,072	93,800
Department of Energy:			
Basic	45,500	45,000	50,100
Applied	9,600	10,900	11,300
Total	55,100	55,900	61,400
USDA Cooperative State Research Service	48,000	46,000	49,000
USDA Agricultural Research Service	24,500	27,000	35,000
Agency for International Development:			
Broad definition	NA*	46,854	43,756
Narrow definition	NA	14,332	6,082
National Aeronautics and Space Administration	NA	6,400	7,200
Veterans Administration	5,400	6,365	9,400
Environmental Protection Agency	3,000	3,400	5,666
National Bureau of Standards	850	3,300	3,300
Food and Drug Administration	3,000	4,700	5,800
National Oceanic and Atmospheric Administration	2,144	2,215	2,680
Small Business Innovation Research**	12,033	12,000	NA

*NA: Not available.

**SBIR dollars are a part of the total spending reported by the above agencies. They should not be added on to total spending.

SOURCE: Office of Technology Assessment, 1988.

is also being made by the Department of Defense, $119 million; the National Science Foundation, $93.8 million; and by the Department of Energy, $61.4 million. The Department of Agriculture expects to fund some $84 million in biotechnology research, divided between the Cooperative State Research Service and the Agricultural Research Service.

Federal support of biotechnology research and development has increased minimally every year since 1984. Although one reason for these increases may be its political attractiveness to agency officials, a more likely explanation is that biotechnology comprises a set of tools that have become fully integrated into the life sciences.

Some 33 States are actively engaged in some form of promotion of biotechnology research and development. These efforts are seen as a means to achieve academic excellence in their colleges and universities or as a path to economic development, or both. **State investment totaled $147 million in fiscal year 1987 (1/16th the Federal investment)**, with three States—New Jersey, New York, and Pennsylvania—making up more than half of that amount. The States employ various funding mechanisms to reach their goals, including issuance of bonds, direct legislative appropriations, allocation of State lottery funds to biotechnology, and mandatory industry and government matching funds.

With the oldest State program, that of North Carolina, only in its sixth year, it is too early to judge the success of State efforts. The only available measures of success are indirect ones, namely, the size of the budget, the number of biotechnology companies within a State's borders, and the extent of involvement by universities and private industry. Although long-term, stable funding runs counter to the pattern of State investment, it is vital in the area of biotechnology. State programs with strong support from their governors appear to hold an advantage, as do those that can manage to avoid fiscal duress, severe unemployment, and educational insufficiencies. States that have an existing base of strong research universities hold the greatest advantage.

The commercialization of biotechnology by U.S. industry remains healthy and competitive. OTA identified 403 American companies dedicated to biotechnology, and 70 established corporations with significant investments in biotechnology. Combined, U.S. industry is spending an estimated $1.5 billion to $2.0 billion annually in biotechnology research and development.

Because biotechnology has become an essential tool for many industries, there is no such entity as "the biotechnology industry." Rather, it is a tool employed by several industrial sectors, each with its own advantages and obstacles in the race to market. Human health care, primarily therapeutics and diagnostics, continues to be the focus of most R&D investments, with chemicals ranking second and agriculture third as fields of application for industrial biotechnology.

Strategic alliances between large corporations and smaller, dedicated biotechnology companies are increasing and are seen as a sign of financial strength by investors. Instability in the financial markets may accentuate the dependence of many smaller firms on large, established corporations. Most large corporations continue to rely on outside sources of innovation, either a smaller firm or a university scientist, with these collaborations benefiting both parties. However, the development of in-house expertise in biotechnology is occurring rapidly in major U.S. corporations.

Training and Employment

The number of jobs in biotechnology has grown rapidly in the past decade. **A 1987 OTA survey of both dedicated biotechnology companies and large established corporations in the United States yielded an estimate of 35,900 jobs in the field, of which 18,600 are for scientists and engineers**. Nevertheless, despite employment growth in recent years, biotechnology is not expected to become a major industrial employer.

Although the supply of specialists in biotechnology appears adequate to meet current demand, shortages in particular areas will occur from time to time. Shortages in such emerging areas as protein engineering have occurred but were largely unavoidable. Anticipated shortages of bioprocess engineers have not yet developed, although the problem could worsen as more biotechnology products reach the later stages of commercialization. Demand for expertise in plant and animal tissue culture and protein chemistry may be outstripping supply, and a growing need for persons to assess the risks of engineered organisms released into the environment has led to a shortage of microbial ecologists.

The mix of personnel at biotechnology companies is changing as production and quality control become more important. The 1987 OTA survey of biotechnology companies found that Ph.D. scientists represent 20 percent of total personnel and 28 percent of scientific personnel. A 1983 survey had found that 43 percent of R&D personnel possessed Ph.D.s. This shift has created more opportunities for biologists and biochemists at the master's and bachelor's degree levels, and will be providing room for those with 2-year associate of applied science degrees.

Molecular biologists and immunologists constitute about a third of the research workers in biotechnology. For the most part, companies see an

Photo credit: Center for Biotechnology, State University of New York, Stony Brook

Recombinant DNA and other new biological techniques are becoming well integrated into science education and training, from high schools to postdoctoral activities. In the workshop shown here, honors-level high school biology teachers are learning the techniques needed to set up DNA laboratories in their schools.

ample supply of scientists trained in molecular biology, biochemistry, cell biology, and immunology as a result of the traditionally strong support for those fields by the National Institutes of Health.

The NIH, by far the largest Federal source of fellowships and training grants, is also the largest supporter of such training for biotechnology. NIH estimates that $70 to $80 million of its training funds support graduate students working in areas either directly or indirectly related to biotechnology, approximately 6,000 students. At the same time, the share of NIH's research budget devoted to training has shrunk from 18 percent in 1971 to a low of less than 4 percent in 1987.

The National Science Foundation sponsors roughly 150 predoctoral fellowships, totaling about $8 million, in the biological and biomedical sciences. Only 20 fellows are funded at the postdoctoral level; these are all in plant biology and environmental sciences, at a total cost of $2.2 million. Other Federal agencies, notably the Department of Agriculture and the National Oceanic and Atmospheric Administration, support varying smaller numbers of students in areas related to biotechnology.

Based on a 1984 survey, biotechnology companies provide between $8 million and $24 million for training grants and scholarships. Industry funding is estimated to account for about 10 to 20 percent of all money for biotechnology training programs. Combined with the contributions made by industry to the research and salaries of trainees at research universities, industry provides financial assistance to about 20 percent of biotechnology trainees.

Colleges and universities have responded fairly rapidly to advances in biotechnology, by creating a range of new programs in biotechnology training and education. OTA has identified 60 such programs at 49 different U.S. colleges and universities. About three-fourths of these programs are based at State institutions.

Seventeen States reported funding university and college training programs in biotechnology. But complexities in accounting procedures and disbursement of such funds mean that few can provide exact dollar figures. For those that did report spending on specific programs, the figures for fiscal year 1987 ranged from a high of $1.3 million in Georgia to a low of $40,000 in Pennsylvania.

Campus-Industry Collaboration

Collaboration between industry and academia has always played an important role in biotechnology research. The industrial contribution to academic research is approximately four to five times greater in biotechnology than in other fields; per dollar invested, industrially supported university research in biotechnology generates four times as many patent applications as does company sponsorship of other research on campus. Nearly half of biotechnology companies support university-based research. Although small compared to the contribution made by the Federal Government, that support has grown by an average of 8.5 percent annually in the first half of the decade.

The nature of this commitment appears to be changing. Few biotechnology companies are planning to invest large sums over long periods for undirected research, as was done in the early 1980s by Monsanto at Washington University. An increasing number of cooperative arrangements represent consulting and contract research rather than long-term partnerships.

The debate over the impact of such collaboration on academic science remains unresolved. With the exception of isolated studies, little evidence exists to either substantiate or refute the claims that such cooperative efforts are undermining the university's mission and independence. As this debate continues, two tradeoffs bear watching:

- whether losses to science or to university values that result from increases in the level of secrecy in universities are offset by net additions to knowledge that result from infusion of industry funds into university laboratories; and
- whether shifts in the direction of the university research agenda toward more applied and commercially relevant projects have benefits for human health and economic growth that far outweigh the risks to basic research.

Collaborative efforts in biotechnology pose specific problems for each group of participants. A recent survey found that faculty receiving industry funds are much more likely than other biotechnology faculty to report that their research has resulted in trade secrets and that commercial considerations have influenced the choice of research projects. In another study, 40 percent of faculty with industrial support reported that their collaboration resulted in unreasonable delays in publication.

For industry, the major issue is whether such collaboration will prove fruitful and hasten the development of new products and processes. The nature of the agreement—specifically, who negotiates the contract and how property rights are assigned—plays an important role in the process and is, therefore, a major concern for companies entering into such agreements.

Added to those uncertainties is the great variation among collaborative agreements. Despite those variations, universities can take several steps when negotiating collaborative agreements to maximize the benefits to all parties and minimize potential risks. Those steps include specifying the scope of the agreement (the research area to be supported and the commitment expected from faculty); maintaining control over the selection, methodology, and review of the research to be undertaken; detailing the sponsor's responsibilities; and spelling out in advance guidelines on proprietary information, publication requirements, patent rights, and income. Apart from continued funding of the academic research that often sets the stage for such collaboration, the mechanics of Federal monitoring of such relationships are not without problems.

Any funding source has the potential to shape the research agenda and influence those who carry out the work. A history of Federal programs, dating from the Morrill Act of 1862 that established the land grant colleges, indicates how universities can be shaped by outside forces. While many early fears about the influence of industrial sponsorship of biotechnology research in university laboratories have not been borne out, the situation warrants monitoring. There remains sufficient concern about the long-term effects of such funds on research agendas, secrecy, conflict of interest, and student education.

Opportunities for Development

There is tremendous variation in the way that States and the Federal Government define and account for biotechnology spending. Also, there is no single model by which industry funds research in the field, nor is there a common approach to the carrying out of commercial developments of biotechnology products. At the same time, each sector affords significant opportunities to foster growth in the field.

At the Federal Level

The activities of the NIH determine to a large extent the nature of Federal support for biotechnology. In recent years the White House and others have increasingly pressured NIH to expand its mission and provide support for more applied research.

In 1986, an NIH committee began to draft guidelines that would permit companies unprecedented access to NIH resources. The guidelines, written in response to the Technology Transfer Act of 1986 (Public Law 99-502), give companies exclusive licensing rights to the fruits of government-sponsored research and encourage scientists to seek commercial applications for their work. This opening of the laboratory doors to commercial application offers great promise to the biotechnology industry, which has long relied on work conducted by NIH scientists.

Although the NIH investment in biotechnology dwarfs that of other agencies, opportunities to foster growth abound throughout the Federal Government. Other agencies, such as the National Science Foundation, the National Aeronautics and Space Administration, the Department of Energy, and the National Oceanic and Atmospheric Administration, fund basic and applied research in biotechnology. Agencies with diverse missions, such as the Departments of Defense and Agriculture, and those with regulatory missions, such as the Food and Drug Administration and the Environmental Protection Agency, fund biotechnology research relevant to their mandate.

Photo credit: Marvin Lewiton

Undergraduate students in MIT's Bioseparations Research Laboratory, funded in part by the National Science Foundation and the National Institutes of Health.

Finally, agencies traditionally viewed as service oriented, such as the Veterans Administration, the Agency for International Development, and the National Bureau of Standards, fund biotechnology research relevant to their service roles. The National Bureau of Standards is a partner in a joint venture with the University of Maryland and Montgomery County, MD, to develop a national resource for biotechnology-related measurement research. A plan developed at the direction of the Senate Commerce, Science, and Transportation Committee estimated that measurement needs will add as much as 25 percent to the costs of biotechnology products, and the Bureau is devoting more than 2 percent of its budget to generic applied and basic research in this area.

The Small Business Innovation Research (SBIR) program has invested more than $36 million in various biotechnology companies since it first awarded grants in 1983. In fact, biotechnology is the leading recipient of SBIR funds, which are derived from a percentage of the budget of every Federal agency that spends at least $100 million on extramural research. SBIR invests more in biotechnology than in information processing and medical instrumentation.

Federal agencies report higher levels of support for applied work in biotechnology in fiscal years 1985, 1986, and 1987, than in 1984. Yet applied research support as a percentage of total R&D support has declined (in constant dollars) across the Federal research budget in the past 5 years. **It is not clear, therefore, whether an actual increase in support for applied biotechnology has occurred or whether agencies have become more proficient at describing work as applied and accounting for expenditures in those areas.**

By itself, greater support does not translate directly into successful ventures. NSF's Engineering Research Centers program expects to devote a growing share of a budget, which could reach $50 million in fiscal year 1988, to biotechnology-related work. Yet the effectiveness of the program has not been proven, and several factors could impede its progress. These factors include the reliance in funding decisions on scientific merit over other relevant criteria, inadequate coordination by Federal officials with State programs and the possibility of competing initiatives, and the lack of clearly defined evaluation and monitoring criteria.

Because Federal agencies seek an array of applications from biotechnology research, a certain amount of redundancy among supported programs is inevitable and probably healthy. At the same time, the goals of various agencies might at times be better met by increased cooperation among agencies wishing to pool their resources on common projects.

At the State Level

States have different expectations about their return on biotechnology investments. Some spend money to strengthen faculties so that universities can better attract private business to the State. Others offer direct incentives, including facilities and tax advantages, to attract small firms. Regardless of approach, successful programs rely on a strong academic and research base, sufficient local venture capital, and an unusually vigorous interaction among researchers, manufacturers and users, and State authorities.

Successful State programs in biotechnology build on previous efforts to attract high technology industries. Thus, it is not surprising that California and Massachusetts lead the nation in the share of biotechnology companies within their

Table 1-2.—State Allocations for Biotechnology R&D, Training, and Facilities

State	FY 86	FY 87
Arizona	$1,170,000	$1,540,000
Arkansas	757,173	800,000
California	2,500,000	2,500,000
Colorado	500,000	500,000
Connecticut	665,000	1,100,000
Florida	5,050,000	7,050,000
Georgia	2,600,000	3,000,000
Idaho	438,800	450,000
Illinois	4,500,000	5,000,000
Indiana	4,000,000	1,029,904
Iowa	500,000	3,750,000
Kansas	162,000	172,000
Kentucky	908,500	896,600
Louisiana	670,000	NA
Maryland	2,600,000	3,900,000
Massachusetts	485,000	935,000
Michigan	6,000,000	4,000,000
Minnesota	1,032,000	1,100,000
Missouri	1,500,000	3,700,000
New Hampshire	150,000	450,000
New Jersey	10,000,000	35,690,000*
New York	34,300,000*	*
North Carolina	6,500,000	6,900,000
North Dakota	1,643,090	1,601,783
Ohio	2,194,787	50,000
Oklahoma	1,584,000	1,542,000
Oregon	350,000	360,000
Pennsylvania	2,848,824	18,035,494*
Tennessee	NA	800,000
Utah	110,000	500,000
Vermont	NA	300,000
Virginia	1,500,000	1,750,000
Wisconsin	190,000	418,000

NA: Not available.
*Indicates multi-year appropriation.

SOURCE: Office of Technology Assessment, 1988.

boundaries, with 27 percent and 13 percent, respectively. (See table 1-2 for levels of investment in all States.)

An NSF program begun in 1978 to ensure greater geographical distribution of research awards has proven to be a springboard for biotechnology efforts in Vermont, North Dakota, Montana, Kentucky, and Oklahoma. While it is too early to assess the extent to which NSF's EPSCoR (Experimental Program to Stimulate Competitive Research) funds will help other States gain a foothold in the field, it is clear that several States had such a purpose in mind when they entered the program.

Most States are not aiming only to woo existing firms from other States. Instead, they have turned to nurturing in-State start-up companies in the hope that they will benefit from the industrial growth of those companies. And, as more companies seek sites for manufacturing facilities, States that could not provide an attractive environment for R&D facilities may be able to compete for the manufacturing facility. Regardless of the approach taken, States will remain dependent on Federal research support to universities to achieve their goals in biotechnology. Those contributions must be tied to the existing economic and academic base within each State.

Although some States may not be able to maintain current high levels of support for biotechnology, sustained commitments are vital for long-term success. Unlike the changes that have come about from growth in other high-tech areas, strategic investments in biotechnology promise to transform a State's entire economy, not just increase its work force temporarily or add to its industrial base.

At the Commercial Level

The boom in biotechnology company formation occurred from 1980 to 1984. During those years, approximately 60 percent of current companies were created, with nearly 70 new firms begun in 1981 alone. Consolidation within the industry and the predominance of a few firms have slowed the formation of new firms; nevertheless, the amount of money invested by larger, more diversified corporations continues to grow.

The range of companies commercializing biotechnology encompasses many traditional industrial sectors. They include pharmaceuticals, plant and animal agriculture, chemicals, energy, and waste management. Table 1-3 lists the primary emphases of biotechnology R&D of dedicated biotechnology companies and large, diversified corporations. Human therapeutics is the primary focus of both groups.

Each sector commercializing biotechnology faces different financial markets, public markets, regulatory requirements, patent issues, personnel needs, and problems in attaining product commercialization. As the tools of biotechnology become integrated into each sector, the paths to commercialization more closely resemble those historically taken for more conventional products.

Table 1-3.—Areas of Primary R&D Focus by Biotechnology Companies

Research area	Dedicated biotech companies #(%)	Large, established companies #(%)
Human therapeutics	63 (21%)	14 (26%)
Diagnostics	52 (18%)	6 (11%)
Chemicals	20 (7%)	11 (21%)
Plant agriculture	24 (8%)	7 (13%)
Animal agriculture	19 (6%)	4 (8%)
Reagents	34 (12%)	2 (4%)
Waste disposal/treatment	3 (1%)	1 (2%)
Equipment	12 (4%)	1 (2%)
Cell culture	5 (2%)	1 (2%)
Diversified	13 (4%)	6 (11%)
Other	31 (18%)	0 (0%)
Total	296 (100%)	53 (100%)

SOURCE: Office of Technology Assessment, 1988.

More than in any other high-technology industry, commercial biotechnology expects R&D to generate revenues. The R&D budget for dedicated biotechnology companies surveyed by OTA averages $4 million per firm, or more than 40 percent of anticipated revenues. For large, established companies investing in biotechnology, the annual R&D budget for biotechnology averages $11 million, a figure that represents one-fifth of their total R&D expenditures. Although nearly every major corporation investing in biotechnology spends some of its R&D budget in house, 83 percent also spend some of their budgets on research conducted by outside firms or by universities.

To date, U.S. dedicated biotechnology companies have raised over $4 billion from private investors, according to one estimate. Yet 80 percent of that investment has been made in 10 companies. Investment in health care applications accounts for 75 percent of all investment. Agricultural applications have received only 16 percent of the total investment.

Dedicated biotechnology companies finance their research in two ways—through equity investments and collaborative ventures. If uncertain financial markets prevail, flexibility in access to equity may become restricted, resulting in an increase in joint ventures with larger more established firms. Venture capital and private equity have been the mainstay of support for start-up companies through 1987. As companies mature, however, they turn to public offerings. OTA found a decreased dependence on private investments, a doubling of U.S. equity holders, and a 10-fold increase in public stock offerings in maturing companies over a typical 5-year period. Dedicated biotechnology firms focusing on therapeutics are more likely to be publicly held than those in other fields, although several agricultural biotechnology firms issued an initial public offering in 1987 as they sought cash to bring their products to market.

Although equity investments also may come from individuals or financial institutions, corporate financing is the fastest-growing type of support. Historically, equity investments by large firms tend to be passive, giving the larger firm the chance to keep abreast of new developments. When these investments do lead to research contracts and product licensing agreements, the larger firm often handles final development, licensing approval, manufacturing and marketing, while the dedicated firm retains patent rights and receives royalties for the sale of the product.

Most industrial alliances occur between U.S. companies rather than between U.S. and foreign firms. Although collaborations with foreign companies may provide dedicated biotechnology firms with better access to international markets, there is a legitimate concern that such alliances could reduce future revenues and growth for U.S. firms. The most common foreign collaboration, when it does occur, is with Japanese firms, overwhelmingly in the application of biotechnology to human health care.

Barriers to Development

The growing concern that U.S. trade policy toward high-technology goods may be compromising national security poses a potential threat to the growth of biotechnology exports. Proponents of tighter controls argue that easing restrictions would give the Soviet Union easier access to Western technology. In the case of biotechnology, some fear that unrestrained exports would enhance the ability of other nations to produce biological warfare agents. On the other hand, opponents argue that strict controls will hamper economic competitiveness. A technical advisory committee within the Department of Commerce was formed in 1985 to address the question of biotechnology exports, but committee efforts to date have been marginal.

Photo credit: Monsanto

Genetically engineered tomato plants are shown being planted by researchers at a Monsanto-leased farm in Jersey County, IL.

The second major factor that could hamper commercialization of biotechnology is regulatory uncertainty. Biotechnology faces a much different and more stringent regulatory environment than do many other high technology industries because, among other factors, it is used by highly regulated industries, such as food and drugs. This environment promises to raise the cost of R&D and, thus, the amount of investment needed to market a product. One issue is whether a product produced using biotechnology will result in higher costs for regulatory review than similar products made using traditional methods. This issue will be resolved differently depending on whether the product is a pharmaceutical, an engineered organism, or a plant.

Other potential barriers to commercialization will also affect investment. With patent protection of biotechnology products a major unresolved issue, many companies have pursued trade secrecy as a short term and more certain strategy to assure protection of their technology. This strategy is not their optimal choice. With respect to antitrust issues, OTA was unable to find any aspect of the problem that could be considered unique to biotechnology companies. The impact on biotechnology of the Tax Reform Act of 1986 (Public Law 99-514) is not clear. Although some tax specialists believe that the revised incentives may affect the distribution of investment, they do not expect them to shrink the total amount of money available. At the same time, the repeal of the investment tax credit is expected to increase dramatically the tax rates in research-related areas. That rise is likely to have a long-term negative impact on biotechnology companies.

A Closer Look at Three Sectors

This report examines three areas of research and development in biotechnology; plant agriculture, human therapeutics, and hazardous waste management. Each is of legislative and regulatory interest to the Federal Government, and each presents a different set of issues for debate. Differences in the state-of-the-art, levels and proportions of public and private support, the effects of regulation, and the degree of commercialization in each area illustrate the necessity of viewing biotechnology as a diversified set of tools affecting a variety of sectors.

Biotechnology as applied to the development of human therapeutics represents an area where there has been substantial Federal support of basic research. As a result, the knowledge base is vast and growing, the commercial aspects enticing, and the regulatory regime similar to that applied to more traditional approaches of drug design and manufacturing. In contrast, plant biotechnology faces a smaller knowledge base due to lower levels of Federal support for basic research in the plant sciences. The commercial applications in the field are less developed, although potentially highly profitable, and the regulatory framework new and evolving. The third case study, biotechnology as applied to hazardous waste management, represents an area of minimum R&D investment by both the public and private sectors. As a result, the knowledge base is small and large scale application nearly nonexistent. Applications of biotechnology in this field tend to be driven by regulation.

Human Therapeutics

Biotechnology has become an integral part of research in the pharmaceutical industry, where the emphasis has already begun to move away from technology development and toward clinical applications. Applications of biotechnology to the development of human therapeutics enjoys a level of public and private funding for R&D that greatly exceeds that in any other sector. Such high levels of support stem from expectations that recombinant DNA and hybridoma technologies will bring about the development of products never before available in the quantities necessary for therapeutic applications. Contributions thus far include the production of naturally occurring human proteins through the use of recombinant DNA technology and the production of monoclonal antibodies from rodent and human hybridoma cell lines; others are expected from the available technologies for making proteins function more efficiently and for creating proteins that do not exist in nature.

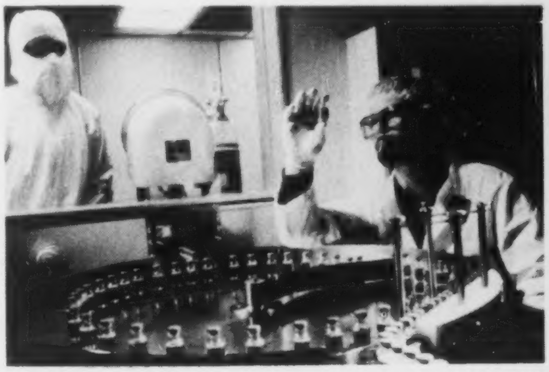

Photo credit: Centocor

Industry scientists sterilize vials for monoclonal antibodies.

In the face of such promise, it is noteworthy that only seven human therapeutics using biotechnology have been approved for marketing in the United States. There are more than 400 biotechnology-based human therapeutics in some stage of clinical trials, comprising less than 2 percent of the 25,000 active applications for investigational new drugs. Nevertheless, of the 20 FDA approvals of new human therapeutics in 1986, four were products of recombinant DNA or hybridoma technology. This high approval rate of biotechnology products is one reason why industry analysts project billions of dollars in worldwide sales of therapeutics made from the new technologies, and should help to sustain or increase the level of public and private investment.

Six major factors will influence the rate of progress in the development of human therapeutics:

- availability of funds for research;
- support of personnel;
- regulation of products made using biotechnology;
- protection of intellectual property;
- access to information generated by research; and
- gaps in basic research.

Plant Agriculture

A critical industry in the United States, agriculture forms a large portion of this country's economy. Research contributes significantly to its success, with an annual rate of return on investment estimated at between 30 and 50 percent. Biotechnology is expected to play a major role in strengthening this important part of the nation's economy. Its tools have the potential to modify plants to resist insects and disease, grow in harsh environments, provide their own nitrogen fertilizer, or be more nutritious. The newer technologies can potentially lower costs and accelerate the rate, precision, reliability, and scope of improvements beyond that possible by traditional plant breeding. But success in this field is by no means assured. Many barriers must be overcome for U.S. agricultural products to remain competitive in world markets.

Of all the problems facing agricultural research, the most pressing is the need for increased Federal support. Only 1.4 percent of the Department of Agriculture's budget is devoted to research. In part, the advent of genetic engineering and related biotechniques has, itself, altered the shape and scope of U.S. agricultural research investment decisions. In particular, the emerging technologies present fundamental challenges and opportunities for the public component of U.S. agricultural research. Widespread commercialization of plant biotechnology depends on breakthroughs in many technical areas that can come only through cooperation with public universities, economic incentives from government, and a favorable regulatory environment. The Federal Government also plays a major role in ensuring an adequate supply of trained personnel.

Basic science advocates charge that the USDA-led system has not been on the cutting edge of science, and has focused research primarily on methods for increasing yield. Other critics have argued that the advent of the biotechnologies has led to private sector, proprietary-dominated research efforts. Others point out that increased private sector research investments have uniquely contributed to the fundamental knowledge base and resulted in a positive economic impact.

Photo credit: Calgene

Cell and tissue culture methods are used to regenerate plant cells containing foreign genes into whole plants.

Biotechnology's impact on the direction of agricultural research has also raised issues about proprietary interests, such as the exchange of plant breeding materials.

Hazardous Waste Management

Waste cleanup is a substantial and growing industry. But the application of biotechnology to waste disposal is still largely experimental, and the investment is small compared with efforts in pharmaceuticals and agriculture. Its potential remains undeveloped due to a variety of technical, institutional, economic, and perceptual barriers. And, more so than in any other industry studied by OTA, the research agenda for waste disposal and management is driven by regulation. The influence of the regulatory regime affects, to a large degree, the extent to which biotechnological applications have been studied. Regulation shapes the field of waste disposal and, thus, provides the impetus for efforts to develop new methods of pollution control. Yet fears of regulatory barriers are discouraging researchers from investigating genetic engineering as a way to discover potentially beneficial organisms.

The Environmental Protection Agency is the lead agency in conducting research and development in waste disposal. But EPA's current investment in R&D in biotechnology is not sufficient to overcome a number of technical barriers in the near future. There is also a widespread feeling that EPA is biased against biological approaches to waste disposal and unwilling to support approaches involving biotechnology. The field lacks credibility because biological techniques were oversold during the 1970s. In addition, many biological approaches take longer than incineration or excavation and are avoided because of a desire to address the problem quickly.

Funding appears to be insufficient and comparatively unstable. The in-house research EPA funds is of high quality, but it is at a relatively low level. At the same time, reports from individual companies lack credibility due to the potential conflict of interest inherent in any company-sponsored research. The Federal Government must take the lead in addressing critical research areas and establishing clearly defined cleanup standards.

Because of these factors, small start-up biotechnology firms usually cannot afford the high financial risk required to achieve progress in the field. The large initial investment needed to develop the appropriate technology, as well as the necessary knowledge base, is another obstacle.

Photo credit: Ecova Corp.

Daily tilling of soil provides oxygen to naturally occurring microbes, enabling them to remediate hydrocarbon-contaminated soil in an enclosed, solid-phase soil treatment facility. Current applications of biotechnology to waste management rely on naturally occurring microbes; the application of genetic engineering to this field remains some years away.

Finally, public acceptance is required to implement biotechnological approaches to waste disposal. The generic fear of genetically engineered organisms may be compounded by the difficulty of containing the waste to be disposed.

POLICY ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

Ten policy issues relevant to U.S. investment in biotechnology were identified during the course of this study. They are:

- Federal funding for biotechnology research;
- balancing support for basic and applied research and development;
- interagency cooperation in support of biotechnology;
- information needs and reporting requirements;
- training biotechnology personnel;
- monitoring university-industry relationships in biotechnology;
- Federal support of State programs in biotechnology;
- providing financial incentives for private investment in commercial biotechnology;
- providing direct support for start-up and scale-up in commercial biotechnology; and
- Federal controls on the export of biotechnology products and processes.

Associated with each policy area are several issues that Congress might consider, ranging from taking no action to making major changes. Some of the options involve direct legislative action. Others are oriented to the actions of the executive branch but involve congressional oversight or direction. The order in which the issues and options are presented should not imply their priority. The options provided for each issue are not, for the most part, mutually exclusive: adopting one does not necessarily disqualify others in the same category or within another category; however, changes in one area could have repercussions in others. **Finally, and of critical importance, many of the issues are more germane to certain sectors, such as human therapeutics, plant biotechnology, or hazardous waste management. In those cases, specific issues and options are presented at the end of chapters 9, 10, and 11.**

ISSUE 1: Should current levels of Federal funding for biotechnology research and development be altered?

An issue central to the findings of this report pertains to the adequacy of Federal support for R&D relevant to biotechnology. There are no objective and reliable measures for determining whether current Federal support for biotechnology R&D is sufficient. Clearly, intensive and sustained Federal investment in applications of biotechnology to the life sciences has been transformed into commercial products in some industries much faster than in others. Commercial applications are more advanced in areas such as human therapeutics, diagnostics, and chemicals than in plant and animal agriculture, or bioengineering for waste degradation. In some cases, the slow progress is due to insufficient funds for basic research; in other cases, potential products are simply not being developed because industry does not consider the biotechnology product or process sufficiently better (either functionally or economically) than those that already exist. Furthermore, excessive regulatory burdens or public perceptions associated with applications of recombinant DNA research can be more important factors than underfunding in some biotechnology applications, most notably in plant agriculture.

Option 1.1: Take no action.

Congress may conclude that Federal levels of investment in R&D over recent years have adequately supported the forward integration of biotechnology into many sectors, suggesting steady levels of support as the best approach. The continuance of existing funding patterns, however, will perpetuate current disparities in research emphases.

The current focus of biotechnology application on human health care products is due, in part, to the steady and high levels of funding for biomedical research. However, research applicable to medical biotechnology has moved only recently from technology development into new clinical applications; without Federal funding increases, this transition could be more difficult.

Maintaining the existing funding level for biotechnology research targeted to agriculture could result in a static agricultural sector that is unable to respond to future economic, technological, and scientific needs—both domestically and internationally. Basic knowledge in the plant sciences, for example, would continue to remain in short supply. The barrier to commercialization created by this lack of knowledge would increase. Inadequate funding could also slow some areas of research to help alleviate surpluses, provide new options for the small farmer, result in better products, and make farm practices more environmentally sound.

Biotechnology for waste management has suffered in recent years from a variety of funding and institutional barriers. Its development is in a relative state of infancy compared with that of biotechnology in pharmaceuticals and agriculture. Without sufficient funds, adequate efficacy and efficiency demonstrations will not be carried out, and EPA is not likely to develop sufficient in-house professional expertise for the assessment and regulation of bioremediation techniques.

Particularly underdeveloped areas of biotechnology research could remain stagnant in the absence of additional funds. These areas include: the exploitation of marine organisms to obtain new sources of potential pharmaceuticals, industrial chemicals, and materials; and the development of new biotechnological applications, such as conversion of biomass to fuel and biological sensors for use in measurement devices and bioreactors.

Option 1.2: Decrease existing budgets.

Due to current fiscal constraints, Congress may conclude that it is necessary to cut Federal funding of biotechnology research. Such a decision is more likely to be a consequence of overall reductions in R&D budgets, of which biotechnology would be a part. Reductions in Federal support for biotechnology could slow the transfer of basic research results to applied areas and would require greater private investments in basic research.

Congress could determine that funding of health-related applications of biotechnology is disproportionately high, and reduce funds in these areas. A targeted reduction of research funds for biotechnology applications to human health could have undesirable consequences for non-medical sectors, however, because advances in biotechnology continue to emerge from NIH-funded research that have immediate applications to agriculture, marine biology, the use of micro-organisms in waste management, and many other fields.

Some areas of research, currently underfunded, would suffer disproportionately. For example, Federal support for biotechnology R&D in waste treatment is so minimal now that decreases will further retard new developments. If Congress determines that Federal investment in plant biotechnology is excessive, it could decrease allocations for this sector. However, decreased funding for agricultural research and training would result.

Option 1.3: Increase existing budgets.

Congress could conclude that because of its social, economic, and strategic importance, the rapid development of biotechnology and its transfer into many sectors warrants increased Federal R&D support. Increases could expand the knowledge base necessary for applied research and development and could result in more rapid commercialization of biotechnology in some fields.

Funding increases in the application of biotechnology to basic and applied research relevant to human health might be aimed at some of the important bottlenecks, including research in protein structure and function, protein engineering, the role of natural chemical modifications of proteins in protein stability and function, and development of novel delivery systems for protein drugs. Additional support in many of these areas should continue to yield generic applications—contributing to uses in the pharmaceutical industry as well as chemical, agricultural, and other diversified industries.

Congress could determine that present spending for agricultural research is insufficient. If Congress increases agricultural research funding, plant biotechnology is likely to benefit. The basic science base in the plant sciences is seriously deficient.

Congress could provide additional funds for EPA to develop innovative waste cleanup technologies, particularly those derived from biotechnology. Without increased funds, EPA will continue to emphasize funding of risk assessment studies on micro-organisms containing recombinant DNA, while other high priority projects continue to be supported at relatively low levels.

Increased funds for the application of biotechnology to renewable biomass resources, and for the exploitation of marine biotechnology, currently funded primarily by DOE and NOAA, respectively, should enhance the United States' role in developing these novel uses.

Option 1.4: Reallocate existing funds.

Should Congress conclude that present funding levels are adequate or, because of fiscal constraints, must remain the same, then it could direct that Federal resources be reallocated. Although the budgetary process works against centralized research planning, Congress could decide that pressing needs for advanced R&D in specific industrial sectors warrants a shift of emphasis in research support. This option, however, promotes a degree of instability in patterns of research support in that political and temporal influences could overly bias the National research agenda.

ISSUE 2: Are current emphases on basic v. applied and multidisciplinary research appropriate?

Anecdotal evidence suggests that the current system of research support in the U.S. sometimes fails to fill critical gaps in basic research related to biotechnology and development. Gaps could be filled through additional financial support for applied research, technology transfer, and increased Federal support for multidisciplinary research programs.

Option 2.1: Direct Federal agencies to dedicate more of their budgets to applied and multidisciplinary research in biotechnology.

This option would not necessarily require new funds but would direct agencies to identify areas of applied research in biotechnology in which awards could be made. Applied areas deserving increased funding could be identified by committees of peers comprised of government, academic, and industrial scientists. In addition, areas of research that require multidisciplinary involvement could receive higher levels of support.

For example, at the NIH, support for individual investigator-directed, basic research projects in disciplines underlying medical biotechnology—such as cell biology, immunology, virology, neurobiology, structural biology, and genetics—could be redistributed to multidisciplinary programs involving researchers from several of these disciplines. Possible mechanisms for implementing this approach might involve Congressional reallocation of single investigator awards to center grants (center grants are common in the categorical institutes but not in National Institute for General Medical Sciences). An alternate approach would require that NIH contribute to health-related multidisciplinary projects funded by other agencies, such as the NSF-administered Engineering Research Centers and Biological Centers Programs. Congress might also reallocate NIH funds to create centers and programs that have not moved as rapidly as desired with funds from individual agencies. Such a program is already in place, for example, to apply new methods in structural biology to AIDS vaccine development.

Historically, agricultural research has been applied. The applied nature of the land grant system, combined with a decentralized structure that includes local agricultural experiment stations and extension services, provides a unique national capacity to identify and solve local or regional problems. Reallocating resources away from formula-based funding would diminish the role that even the smallest, poorest funded land-grant universities play. Congress could protect the applied orientation of agricultural research by maintaining strong formula-based funding at the expense of competitive research funding, which is directed towards basic research. Because the database for plant sciences is sparse, however, decreasing awards that foster excellence in basic research could hinder rapid progress in plant biotechnology.

To support more applied work applicable to hazardous waste management, Congress could direct EPA to devote more funds to applications research in demonstration and evaluation. Comparative data on the efficacy, economics, and environmental safety of biotechnical versus other methods is lacking. Additional efforts in testing and evaluation would significantly assist industry development, resolve issues relating to efficacy of specific techniques, and, along with regulatory changes, promote private sector investment.

Any effort to increase emphases on applied research carries the risk of harming the support base for basic science, the source of new ideas. Each agency needs to consider the balance of support between basic and applied work within its mission. Service-oriented agencies, such as the Agency for International Development and the Veterans Administration, report that they emphasize applied research, which best supports their mission. Recent efforts to support more applied and multidisciplinary research at the National Science Foundation indicate a shift in the historical mission of that agency. Such shifts are viewed with skepticism and encouragement, depending on the observer's outlook.

Option 2.2: Require agencies to report on the extent to which the goals of the Federal Technology Transfer Act of 1986 (Public Law 99-502) have been met.

Under The Federal Technology Transfer Act of 1986, directors of government operated Federal laboratories may enter into collaborative R&D agreements with other Federal agencies, State and local governments, industrial organizations, and nonprofit organizations. Biotechnology is an area of research currently pursued in many Federal laboratories that could be more effectively shared with industry and universities through active compliance with Public Law 99-502. As one means of encouraging compliance with the intent of the law, Congress could request that agencies document the extent to which this has occurred within their laboratories.

ISSUE 3: Should there be more interagency cooperation in funding biotechnology R&D?

Some redundancy and duplication of effort is essential to a healthy research enterprise. However, more formal cooperation between agencies in areas of shared interest could facilitate more rapid advances in some areas of biotechnology lacking sufficient or focused support.

Option 3.1: Establish an interagency coordinating body to identify areas of research that could be co-funded across agencies, address solutions to filling research needs, and develop strategies to promote technology transfer.

Congress could conclude that this option would reduce some redundancy in Federal research efforts in biotechnology and promote cost savings. This type of cooperation might best be implemented through a cross agency coordinating body that meets regularly to discuss shared areas of research interest in biotechnology. At present, such coordination is rare and informal.

Applications of biotechnology to human health enjoy the highest levels of Federal funding. The overall medical biotechnology research agenda is evolving from research funded almost exclusively by the National Institutes of Health, with additional contributions from the National Science Foundation, the Department of Defense, and the Department of Energy. A coordinated effort by these agencies is essential if unnecessary duplication is to be avoided and the technological gaps impeding medical applications of biotechnology are to be removed.

A recently formed cooperative effort in plant sciences was initiated by the Office of Science and Technology Policy. The Plant Science Initiative, to be co-funded by the National Science Foundation, the Environmental Protection Agency, and the Department of Agriculture, aims to address gaps in research areas of common interest to each agency.

Advances in the use of bioengineering in waste clean-up could benefit from this type of coordinated approach. For example, EPA, NIH, NSF, the Department of the Interior, the Department of Energy, and the Department of Defense have significant programs related to bioengineered waste cleanup technologies. An interagency coordinating group could identify major gaps in the research and work to prevent unnecessary duplication of efforts by Federal agencies.

ISSUE 4: Are information requirements for informed decisionmaking about Federal support of biotechnology R&D and training being met?

Currently, information about Federal support for biotechnology research and training is scattered and inconsistent. Systematic evaluation of total Federal spending and a direct comparison of spending in specific areas across multiple agencies are complicated by the definition of biotechnology each agency employs and by the method of accounting for expenditures.

Option 4.1: Direct Secretaries and Administrators to report regularly on biotechnology activities.

The Congress could conclude that strategically important areas, such as biotechnology, are important enough to the Nation's economic growth that a more systematic accounting of Federal investment in supportive research is warranted. Authorization Committees could direct individual agencies to develop more routine systems of accounting for spending in specific areas, such as biotechnology, so that overall trends and possible necessary actions can be identified. Some agencies, such as the National Science Foundation and the National Institutes of Health have already adopted such mechanisms. Regular and institutionalized reporting on levels of funding for research and training could promote a more coordinated approach to setting strategies for biotechnology development.

Option 4.2: Direct Secretaries and Administrators to agree upon a uniform definition of biotechnology.

The adoption of a uniform definition could resolve vagueness in future policy development and would allow for more direct comparisons of research support across agencies.

However, Congress could decide that in the absence of any comprehensive mechanism for affecting total Federal spending in biotechnology, there is no sound reason to request that all agencies funding and conducting biotechnology R&D adopt a uniform definition of biotechnology. Given the various and diverse missions of the agencies, flexibility in definition may be desirable. This argument might not apply to reasons to adopt uniform terminology for the purpose of regulation. Also, given the rapid advances in research, any definition would have to be flexible enough to accommodate new technologies or would soon be obsolete.

ISSUE 5: Are Federal efforts in training and education for biotechnology sufficient?

Federal funds, directly and indirectly, support a significant amount of training and education for biotechnology. Most of these funds are directed at research rather than training, but contribute to training nonetheless.

Option 5.1: Take no action.

Training and education for biotechnology in the United States is strong, successful, and well supported. For the most part, personnel needs for the industry are being met. While shortages have been difficult to predict in advance, they have been short lasting when they have occurred. By and large, the current system is working well, though additional support in specific areas could pay off significantly. If Congress takes no action, the United States can expect to continue to enjoy high quality personnel in the biological sciences, but certain needs may not be met and the fit between personnel needs and availability may not be optimal.

Option 5.2: Require Federal agencies to direct more funds for training.

While NIH, USDA, NSF, and other Federal agencies provide substantial research funds, which contribute indirectly to training, training grants and fellowships are less well funded and have declined in recent years. In molecular biology, competitive training grants have effectively encouraged university departments to establish coherent training programs and enable money from faculty research grants to be used for research rather than salaries. Training grants in particular areas of possible need, such as bioprocess engineering, plant molecular biology, microbial ecology, and protein crystallography, could be given special consideration.

Option 5.3: Increase funds for the National Science Foundation or other Federal agencies to provide equipment for biotechnology education and training programs.

Equipment and instrumentation for biotechnology training and research is expensive. Almost every program contacted by OTA reported unmet needs for equipment and facilities. Direct Federal support for R&D equipment and physical plant has been declining, leaving many universities with outmoded equipment. Direct support for instrumentation in biotechnology could provide many programs with much needed equipment, enabling them to train students on state-of-the-art equipment used by industry. Such funds may also encourage researchers from related areas, such as chemistry and engineering, to collaborate in biotechnology research.

Option 5.4: Establish programs to foster the interdisciplinary education needed for most applications of biotechnology.

Peer-reviewed, individual investigator initiated grants provide the bulk of funding for basic research but may be biased against the interdisciplinary nature of many research projects in biotechnology. Interdisciplinary programs could foster the interaction among various fields needed to improve research and training for biotechnology and promote technology transfer across fields and industrial sectors. Congress could encourage agencies to more actively support programs that foster multidisciplinary training in areas related to biotechnology.

Option 5.5: Request the National Academy of Sciences to assess comprehensively future personnel needs in biotechnology.

Given the long time needed to prepare individuals for careers in biotechnology, it is important at both the national and the individual level to be able to anticipate personnel needs several years into the future. The Committee on National Needs for Biomedical and Behavioral Research Personnel of the Institute of Medicine has twice systematically investigated personnel needs in biotechnology by surveying U.S. biotechnology companies. These surveys provide important information on recruitment difficulties faced by biotechnology companies, assist policymakers in setting appropriate funding levels, and enable students to make more informed career choices. Though the Committee was able to make these studies in 1983 and 1985, funds were not available for a similar study in 1987. The National Academy of Sciences could update and expand this work by seeking additional information from the U.S. Department of Agriculture, the Environmental Protection Agency, and the National Institutes of Health on medical, agricultural, environmental, and other personnel needs in biotechnology and the role of predoctoral versus postdoctoral support as it affects the pool of available biotechnology personnel.

Such personnel forecasts, however, depend on assumptions about gross national product, demographic trends, government policy decisions, technological innovation, foreign activities in the field, and other factors that cannot be known with certainty. Given the uncertainty of many of the assumptions that must be considered in making forecasts about labor demand, making such forecasts may be futile. OTA has concluded in previous reports that predictions of shortages should be treated with skepticism. Market forces often significantly alleviate any shortages that do develop. It may be that accurate forecasts of future needs are neither possible nor necessary.

ISSUE 6: Should Congress set guidelines for university policies on industry-sponsored research?

Industrial sponsorship of university-based biotechnology research has become a widespread and generally accepted phenomenon over the past five years. These relationships have provided additional resources for R&D and training in university laboratories, and appear to have facilitated technology transfer into industry. Some of the early fears concerning the potential for skewing the research agenda toward more applied work, increased secrecy among scientists, and negative influences on the educational process have not been realized. Yet there remains concern that if public funds for basic research decline, universities may become more reliant on private funds, possibly allowing some of these fears to be realized.

Option 6.1: Take no action.

Because there is little empirical evidence that university-industry relationships in biotechnology have had significant adverse effects, Congress may conclude that no action is necessary. Most universities whose faculty have entered into contractual agreements with industry have already developed institutional guidelines regulating such agreements. These agreements appear to be satisfactory to participating parties. In addition, most parties continue to be optimistic about the goals of these relationships and are more comfortable with them than they were 10 years ago. Congressional action might stifle interchange between academe and industry.

On the other hand, most Federal research dollars are spent on university campuses. Allowing individual institutions to self-police these relationships while continuing to receive Federal funds could diminish public accountability.

Option 6.2: Require Federal granting agencies to request that universities receiving Federal research money file guidelines for faculty-industry contracts as a condition of receipt of funds.

To ensure that Federal funds are not being used to support research that becomes overly secret or proprietary, Congress could direct agencies to require universities to submit guidelines regarding faculty consulting and contractual agreements. Most research universities have already developed such guidelines. Under this option, those that have not would be forced to do so. While this option would not guarantee that undue secrecy or conflict of interest would not occur, it would encourage universities to set clear policies regarding limits of acceptability for faculty-industry interactions. In addition, this option is consistent with requirements that universities file statements of assurance that other areas—such as protection of human and animal research subjects—are being monitored.

On the other hand, while this approach could raise the accountability level of universities and scientists receiving Federal funds, it could add a layer of bureaucracy to an already burdensome grants process.

Option 6.3: Ensure that a minimal level of facility and equipment needs are being met by public funds to decrease the potential for disproportionate university reliance on private funds.

Industrial sponsorship of research augments public funding, but contributes only partially to the unmet capital needs of universities. Congress could decide that in order to avoid the consequences of some universities relying disproportionately on industry for research funding, adequate levels of construction and equipment grants should be available through granting agencies. This option would not prohibit or discourage universities from seeking industrial funds but would free them from undue reliance on the private sector.

Some would argue, however, that the private sector should make a **larger** contribution to university research if it wants to reap its benefits. Increased public subsidies for university research will allow industry to make even less of a contribution than it already does.

ISSUE 7: Do State efforts in biotechnology need Federal assistance?

There are few mechanisms by which the Federal Government can properly assist State programs in biotechnology. Historically, those States receiving large percentages of Federal research dollars through their universities have held an advantage over those that have received less. In an effort to address distribution inequities, the National Science Foundation initiated the Experimental Program to Stimulate Competitive Research (EPSCoR) to assist States in the development of science and technology programs. The EPSCoR program has helped some States gain a foothold in biotechnology.

Option 7.1: Take no action.

Congress could conclude that Federal assistance for State efforts in biotechnology is unwarranted. The EPSCoR program has assisted those States with historically lower levels of Federal research support in developing new programs in biotechnology, as well as many other fields.

Option 7.2: Direct the NSF to consider an extension of the time frame for EPSCoR grants.

Under the provisions of the current EPSCoR program, qualifying States receive 5-year continuing grants for program development. At the end of the 5-year period, funding ends. Under other programs at NSF, such as the Engineering Research Centers and the Science and Technology Centers, grant recipients demonstrating outstanding achievements are eligible for a new 5-year grant at the end of the first five years. This is not the case in the EPSCoR program. Because it is likely to take longer than five years to establish a new program at the State level, EPSCoR recipients that can demonstrate progress should also be eligible for continued funding after five years. This would allow the stability necessary for States to build the support and infrastructure required for a successful program.

ISSUE 8: Should the Tax Reform Act of 1986 (Public Law 99-514) be amended to provide greater incentives and assistance for firms commercializing biotechnology?

Option 8.1: Take no action.

The tax measures of the Tax Reform Act could remain as they are. These provisions include: extension and reduction from 25 to 20 percent of the R&D tax credit; repeal of the investment tax credit for equipment investment; and abolition of the preferential treatment for capital gains. Due to current fiscal stress, Congress may determine that the provisions of the Tax Reform Act of 1986 are equitable. However, if as a result of some of these measures, the level of private investment in biotechnology is reduced, there will be a negative effect on the level of innovation. This will manifest itself in decreased equipment and capital investment.

Option 8.2: Make the R&D tax credit a permanent part of the U.S. Tax Code and increase it from 20 percent to its original 25 percent incremental rate.

The purpose of the tax credit is to provide an incentive to companies to increase their commitment to industrial R&D. The R&D tax credit was renewed when it expired in 1985. The credit will again expire at the end of 1988. At this time, Congress could grant the R&D tax credit permanent status. A permanent credit would reduce the uncertainty that exists for industrial R&D planners concerning the credit's future existence. In addition to permanent status, Congress could restore the credit to its original level of 25 percent. This was the level adopted in the 1981 Economic Recovery Tax Act (Public Law 97-34).

Option 8.3: Offer the R&D credit to start-up dedicated biotechnology companies.

The structure of the R&D credit currently provides a 20 percent credit for expenditures in excess of the average amount of R&D expenditures for the previous three years. The purpose of the incremental credit is to provide incentives to companies to increase research expenditures. Companies that do not have a 3-year expenditure base are not eligible for the R&D credit as it is currently structured.

Congress could offer a refundable credit to start-up companies in the year earned. A refundable tax credit would be more valuable to biotechnology start-ups in the year earned than a tax credit carried forward to the years in which enough taxable income would be earned to take advantage of the credit.

Option 8.4: Make the basic research tax credit a permanent part of the U.S. tax code.

The basic research tax credit, an incentive included in the 1986 Tax Reform Act, encourages companies to increase spending on basic research at universities and other non profit research institutions. It is seen as a mechanism to encourage cooperative relationships between industry and universities. On contractual research, the credit equals 20 percent of the company's total contract research payments over a fixed base. A permanent credit of this sort would reduce future uncertainties associated with this tax incentive.

Option 8.5: Restore the preferential treatment of capital gains incurred under Research and Development Limited Partnerships (RDLPs).

Under the new tax law, capital gains are treated as ordinary income. The former treatment of capital gains attracted investors to RDLPs because the gains from the sale of a limited partnership were treated better than the dividends themselves. Because RDLPs represent a large portion of the investment in biotechnology, Congress could reinstate the preferential treatment of capital gains for investors in RDLPs. This would restore incentive for investors to pursue this investment option, thereby increasing private investment in the biotechnology industries.

ISSUE 9: Are Federal mechanisms for assisting biotechnology firms in obtaining the financing necessary for start-up and scale-up adequate?

To date, venture capital and private equity placement have been the mainstay of biotechnology start-ups. Nearly all dedicated biotechnology companies in existence have received venture capital. As firms mature, they turn to public offerings and corporate equity investment as sources of funding. There are inherent risks to overdependence on any of these sources. Venture capital sources may become restricted because of fluctuations in the economy. The risks of reliance on the public markets to finance scale-up and production may be too great for firms caught in a downturn in the market. To ensure the continued growth and maturation of biotechnology companies, Congress could decide that more aggressive action is needed to assist biotechnology companies in two critical stages—start-up and scale-up. Support of industrial innovation could, in part, finance areas of applied research and development not already supported through the Federal research agencies.

Option 9.1: Take no action.

Congress could decide that the growth of biotechnology companies has been a result of creative financing through available sources of capital. Congress could conclude that sufficient investment capital is available to commercialize biotechnology and the Federal Government need not intervene at this time.

Some have argued that traditional policy discouraging government subsidies for industrial innovation places the United States at a disadvantage compared to other industrial nations, which have targeted funds to support industrial biotechnology. Allowing the marketplace to remain the sole influence over the health of these industries may be detrimental in the long run.

Option 9.2: Direct the Small Business Administration to evaluate programs under existing authority that could provide a source of venture capital funding for small businesses, biotechnology included.

The Small Business Investment Act of 1958 authorized the Small Business Investment Company, or SBIC Program. SBICs are privately capitalized, owned, and managed investment firms that provide equity capital, long-term financing, and management counsel to new and expanding small business concerns. They are licensed and regulated by the Small Business Administration and can borrow funds from the Government on a long-term basis for reinvestment in small business. SBICs, however, have faced uncertain congressional funding and restricted access to capital markets. To insure continued availability of venture capital for biotechnology, the Small Business Administration, with proper authority, could form a quasi-governmental corporation that would raise money in the private sector to be used as a venture capital fund for start-ups. The SBA could evaluate the success of the SBIC program and make recommendations for its improvement.

ISSUE 10: Is the current export control system as dictated by the Export Administration Regulations working efficiently in the approval of biotechnology products for export?

The Departments of Commerce and Defense each play important roles in the export control process. The DOC monitors the Commodities Control List (CCL) and the DoD monitors the Militarily Critical Technologies List. Each agency brings to the process a different philosophy on what export controls should accomplish. As more and more biotechnology products become available for export, there is some concern on the part of industry that these products will become caught between the interests of Commerce and Defense, or will become delayed due to administrative confusion about the required approval process for biotechnology products.

Option 10.1: Take no action.

Congress could determine that the current export control system as dictated by the Export Administration Regulations is working efficiently, and has achieved a sufficient balance between economic and national security interests. The 1985 amendments to the Export Administration Act (EAA) addressed several issues that were not covered in the original EAA. For example, foreign availability and decontrol were two items that were to be emphasized by the agencies. However, little progress in the reduction of the CCL has been made.

Maintaining the current CCL could adversely affect the U.S. position overseas because it is often viewed by U.S. and foreign industry as encompassing too many products and technologies, making it difficult to manage. Continued operations under the present system could hamper efforts to promote U.S. products abroad and penetrate valuable foreign markets. The final outcome could be migration of U.S. industries abroad to avoid U.S. export regulations.

Option 10.2: Congress could decide that the present export control system is adequate and could request that even greater controls be enacted.

Those in favor of greater controls are concerned that our national security would be compromised by reduction of the CCL and decontrol of goods even when foreign availability is documented. Once foreign availability is documented, decontrol can be withheld while negotiations are pursued with supplier countries. The result has been that few items have completed the procedures necessary for decontrol and removal from the CCL.

Congress could request that the agencies involved in the export control process maintain stricter control over exports. For the biotechnology and other high-technology industries, this could result in the loss of valuable overseas markets to foreign competitors in Western Europe and Japan. This may also provoke overseas migration of companies who do not want to be burdened with U.S. unilateral export controls.

Option 10.3: Direct the Secretary of Commerce to evaluate the efforts of the Biotechnology Technical Advisory Committee (TAC).

The Biotechnology TAC began in early 1985 to advise agencies involved in export control on technical matters and new developments in the biotechnology industries. The TAC can make recommendations to the Department of Commerce on items to be removed from the CCL. This mechanism of communication between the biotechnology industries and those in charge of export control policies is valuable to both parties. The TAC can give important technical information to the actors involved in controlling biotechnology exports. Thus far, however, the TAC has submitted recommendations of items to be decontrolled and has seen no results. Because the decontrol process is often held up for national security reasons, few items have been removed because of foreign availability. Congress could request the Department of Commerce to review the TAC, with the intent to develop recommendations for improved use of the TAC mechanism.

Chapter 2

Introduction and Overview

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Chapter 2

Introduction and Overview

INTRODUCTION

For more than four decades, American political tradition has called for strong Federal support of basic research. In contrast, Federal support and policies related to applied research have been inconsistent—more related to changing national security needs, and more reflective of global economic competitiveness and differing political views. While the debates over Federal support of basic research were essentially settled in the affirmative in the late 1940s, debate over technological development and application has continued over the years, often technology by technology. In recent years, a new dimension has been added to the debates, stimulated by the belief that the United States has suffered some loss of international economic competitiveness due to the relative decline in its scientific and technological capabilities.

This new dimension is reflected in keen interest in and a focus on questions related to the Federal Government's roles and policies in supporting, affecting, and facilitating the levels and patterns of industrial innovation. Much of this interest arises from the belief that the ability of the United States to improve and maintain its present standard of living depends on its ability to maintain and enhance its competitive position in the provision of goods and services derived from application of advanced industrial technologies. Debates on these issues in the context of various high technologies, such as biotechnology, are likely to continue in the times immediately ahead due to concerns about the trade deficit and U.S. industrial competitiveness.

Far more than an opportunity for economic predominance in biotechnology is at stake. **The wide-reaching potential applications of biotechnology lie close to the center of many of the world's major problems—malnutrition, disease, energy availability and cost, and pollution.** Biotechnology can change both the way we live and the industrial community of the 21st century because of its potential to produce:

- products never before available,
- products that are currently in short supply,
- products that cost substantially less than products made by existing methods of production,
- products that may be safer than those now available, and
- products made with raw materials that may be more plentiful and less expensive than those now used (4).

Policymakers are interested in biotechnology because of its potential for improving health, food production, and environmental quality, and because it is seen as a strategic industry with great potential for heightening U.S. international economic competitiveness. These expectations logically lead to questions of whether current levels of funding are adequate and properly focused and whether the United States should use additional methods to promote research and development in this diverse area. As in other areas of science and technology, there are fundamental questions about the obligations and roles of various institutions in promoting and regulating these technologies. Traditionally, basic research has been supported by the Federal Government, applied research and development has been the domain of industry, and the States have invested in both, depending upon the needs of their economies.

The ubiquitous nature of biotechnology makes it the focus of several areas of public policy. Biotechnology relies on the expertise of a multitude of collaborative scientific and engineering disciplines in both the basic and applied sciences, requiring support across a wide range of fields. The multidisciplinary nature of biotechnology has extensive implications for governmental, educational, and industrial structures, suggesting diverse incentives for action. The allocation of resources to build the necessary scientific and technological base and to provide for the regulation and control of resulting products, processes, and uses is a fundamental role of government.

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The tools of biotechnology allow manipulation of biological organisms in ways that will greatly increase their utility, thereby motivating industrial applications. Furthermore, the Nation's educational institutions are affected by biotechnology because of its dependence on strong research capabilities, a highly skilled workforce, and its encouragement of intersectoral relationships.

While biotechnology has taken on a "trade" status, with its own firms, newsletters, investment funds, and regulations, it is not a single industry but a set of enabling technologies applicable to a wide range of industries. As full integration of biotechniques occurs, each sector of industry developing biotechnology-based products will face different opportunities for and barriers to commercialization. The ability to recognize similarities and differences between sectors will be critical to policymaking as new products are ready for marketing and strategies for promoting and regulating biotechnology products are developed.

Because these advances make significant commercial and social gains possible, government and industry share an interest in promoting biotechnology research and development. This report examines the current level of investment in biotechnology research, development, and training by Federal and State Governments, industry, and collaborative arrangements among sectors. It also describes the nature of the research being funded and identifies scientific and institutional gaps and barriers to developing this new set of technologies. **This report focuses on the positive and negative financial, human, scientific, and institutional inputs into the development of biotechnology.** As the title of the report implies, spending allocated to the development of biotechnology can be considered an investment because of expectations that resources so dedicated will result in future benefits. Much more difficult to assess is whether expenditures are reasonable for future growth and whether expenditures are proportionate to those being made in addressing other national needs. Finally, to understand the reasons for investment in biotechnology, the ultimate products of research and the paths to application are also discussed in three case studies.

The following section discusses the definitional issues surrounding biotechnology and describes the problems associated with accurately assessing U.S. investment in biotechnology.

ASSESSING U.S. INVESTMENT IN BIOTECHNOLOGY: LAYERS OF COMPLEXITY

In preparing this report, OTA estimated levels and directions of U.S. investment in biotechnology by surveying Federal agencies, State agencies, and private industry. In addition, four workshops were held with attendees from Federal, State, and local governments, industry, and academia (see app. C for workshop participants). The first workshop, titled "Public Funding of Biotechnology Research and Training," was held in September 1986 (10). Representatives of Federal and State agencies presented budget data for biotechnology and discussed the implications of the varying definitions of terms. OTA obtained updated budget information in fall 1987.

In April 1987, representatives from academia and industry met at OTA to discuss "Collaborative Research Arrangements in Biotechnology" (3). In June 1987, biotechnology industrialists were convened to discuss "Factors Affecting Commercialization and Innovation in the Biotechnology Industry" (5). Finally, in July 1987, a workshop was held to discuss "Public and Private Sector Roles in Funding Agricultural Biotechnology Research" (11).

The OTA surveys, workshops, and informal communications with representatives of all sectors interested in biotechnology revealed two methodological dilemmas in assessing U.S. investment in biotechnology: variation in the definition used to describe biotechnology and variation in the methods used to account for biotechnology investment. Each of these difficulties is discussed below.

Defining Biotechnology

In a 1984 report, after extensive canvassing of academicians, industrialists, and government officials involved in biotechnology, OTA arrived at two definitions of biotechnology. The first definition is broad, encompassing both old and new biotechnology, and includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses. Since the dawn of civilization, people have deliberately selected organisms that improved agriculture, animal husbandry, or brewing. **To differentiate between biotechnology using more traditional techniques from the newer techniques developed in recent years, OTA uses a second, more narrow definition of biotechnology. This definition refers only to "new" biotechnology: the industrial use of recombinant DNA, cell fusion, and novel bioprocessing techniques (4). As in the earlier report, the term biotechnology, unless otherwise specified, is used here in reference to new biotechnology.**

Photo credit: Amgen

Preparation of a DNA sequencing gel to analyze structure of a gene for porcine somatotropin.

The current study focuses on R&D investment in fields affected by new biotechnologies. Three main areas of research relevant to biotechnology can be described: basic, generic applied, and applied (4). Basic research involves biotechnology by using its component tools (e.g., recombinant DNA and hybridomas) to study the different ways in which biological systems work and to identify the mechanisms that govern how they work. Included in this category are studies that address such questions as how viruses infect cells, how immunity to pathogens is acquired, and how fertilized egg cells develop into highly complex and specialized organisms. Biotechnology is used in a broad range of scientific disciplines, ranging from microbiology (the study of micro-organisms such as viruses and bacteria) to biophysics (the use of physical and chemical theories to study biological processes at the molecular level). A greater understanding of the mechanisms of evolution and the resilience of ecosystems will also come from new biotechnology.

The phrase "generic applied research" is thought by some to be vague and ambiguous; however, it is useful for describing research that bridges the gap between basic science done mostly in universities and the applied, proprietary science done in industry for the development of specific products. Various groups have coined alternative phrases, such as "bridge" research, "technical" research, and "strategic" research. Examples of generic applied biotechnology research are the development of general methods for protein engineering and large-scale mammalian or plant cell culturing.

Applied research is directed toward a very specific goal. The use of recombinant DNA to develop vaccines for specific antigens, such as malaria or the HIV virus responsible for Acquired Immunodeficiency Syndrome (AIDS); the transfer of herbicide or pesticide resistance to a particular plant species; and the use of monoclonal antibodies as purification tools in bioprocessing are all examples of biotechnology use in applied research.

In the current political environment, where promotion of high technology is strongly favored, the definitions used for biotechnology have important ramifications. The terms used to describe biotechnology can affect research funding and the regulatory treatment of potential commercial products. Some groups believe that any confusion about what biotechnology is could be alleviated by substituting more specific terms such as gene therapy, protein engineering, and bioprocess engineering, for the general term "biotechnology" (1).

A recent General Accounting Office (GAO) report, titled "Biotechnology: Analysis of Federally Funded Research" (2), used three categories to calculate levels of biotechnology funding at five Federal agencies. They are:

1. Basic research in the sciences underlying biotechnology.
2. Applied research and technology development using the new techniques of biological research. This work is done to devise, apply, or improve products and processes.
3. Research pertinent to the regulation of biotechnology products and processes.

It is the second category—applied research—that presents the most confusion in determining the extent of public and private investment in biotechnology.

Since the definition of biotechnology varies among funding sources, figures presented without explanation could create myths that would become difficult to dispel. Therefore, instead of requesting each Federal agency to report funding levels only as they pertain to a uniform definition of biotechnology, OTA asked each to offer its own definition of biotechnology (see ch. 3). For the surveys of industry investment in biotechnology, the respondents were requested to account for research related to biotechnology in general and to each of three specific categories of new biotechnology: recombinant DNA techniques; cell fusion technology; and novel bioprocessing methods.

Photo credit: Cetus

Industrial scientist successfully clones and expresses the *E. coli* methionine aminopeptidase enzyme.

Accounting for Investment in Biotechnology: The Pitfalls

Accounting for U.S. investment in biotechnology is a formidable task. As described above, the definitional dispute adds to the complexity of a process that must also recognize sectoral differences in accounting and reporting. In addition, within each sector—Federal, State, and private—there may be as many differences as there are parties. Within the Federal Government, OTA collected budget data from 11 different executive agencies, each with its own system of accounting for budgets and expenditures. In a survey conducted by OTA, 33 States reported a variety of mechanisms for determining their level of investment in biotechnology. In addition, OTA surveyed small, dedicated biotechnology companies and larger, diversified and established corporations with significant investments in biotechnology, to determine levels of investment, areas of application, number and type of employees, and factors affecting commercialization. Although certain accounting procedures are standardized in industry, those used in reporting R&D can be vague and strategically motivated. Pitfalls specific to the assessment of investment in biotechnology in each sector are summarized below.

Assessing Federal Investment

Aggregate estimates of total Federal support for biotechnology are still rough and preliminary.

There is no easy or systematic way by which Federal agencies can separately account for dollars being dedicated to biotechnology. Because the tools developed from biotechnology have been fully integrated into both basic and applied work in so many areas of research, separating out "biotechnology-related work" is an arduous task with suspect results. Biotechnology draws from established fields such as biology, chemistry, and engineering, and is seldom identified separately in an agency's budget. In addition to differences in mechanisms of accounting for specific research expenditures, agencies vary in their definition of biotechnology, making estimates of total Federal spending speculative, and cross-agency comparisons difficult to interpret.

Assessing State Investment

At the State level, few budgets list research appropriations in general, let alone biotechnology, as a line item in their budget. Research and development funds are derived from several lines in a budget and are directed to several recipients. Thus, undercounting or overcounting can easily occur, depending on the perspective or biases of the accountant. In addition, operating budgets for biotechnology initiatives may be derived from several sources other than State coffers, such as Federal research agencies and philanthropic organizations. States facing this dilemma provided OTA with estimates of investment. Furthermore, as with Federal reporting, the definition of biotechnology used by the reporting States affected how funds were accounted and programs initiated.

Assessing Private Investment

Two problems were faced in evaluating investment by the private sector. First, the identification of firms investing in biotechnology is problematic. Some firms call themselves biotechnology companies when, in fact, they do not fall within the OTA definition. Other, more traditional companies may be conducting important research in biotechnology but do not consider themselves a biotechnology firm, and do not identify themselves as such. Large corporations may be multinational, with several subsidiaries, making identification of programs and budgets complex.

Second, even when a reliable list of firms is available, gathering information from the identified companies is difficult. Firms that are privately held—as defined by the Securities and Exchange Commission—often do not divulge relevant financial information, resulting in inevitable undercounting of dollars devoted to biotechnology. In addition, some forms of investment by public firms, such as research contracts or licensing agreements, need not be divulged, compounding the problem. Thus, any accounting of total private investment in biotechnology is likely to be an underestimate.

ORGANIZATION OF THE REPORT

This report is organized to present U.S. biotechnology investment data in several ways. Chapters 3, 4, and 5 present analyses of investment in biotechnology by the Federal Government, the States, and industry, respectively. Resources dedicated to biotechnology and the implications of the distribution and use of those resources are discussed. Chapter 6 summarizes factors affecting innovation and commercialization of biotechnology. Chapter 7 presents an analysis of university-industry collaboration in biotechnology as an important device used to facilitate research and development. Chapter 8 presents the results of an OTA survey of U.S. training programs in biotechnology and discusses personnel needs in industries commercializing biotechnology.

Chapters 9, 10, and 11 assimilate many of the issues presented in the first eight chapters into a specific industrial framework. Because it is difficult to draw conclusions across all industries regarding the influence of any one factor on biotechnology, OTA analyzed three industries in particular. Chapter 9 discusses U.S. investment in biotechniques applied to human therapeutics. The application of biotechnology to human therapeutics is the first and greatest growth area of applied biotechnology and has matured to the point where more traditional concerns, such as patenting and regulation, are influencing application as much as funding levels. Chapter 10 examines investment in biotechnology applied to plant agriculture and issues that affect the dollar flow into R&D in that field. Plant agriculture is considered to be the next growth area of biotechnology. Finally, the application of biotechnology to hazardous waste management, as the least technically advanced application of biotechnology of the three fields examined, is discussed in chapter 11.

SUMMARY

This report is a comprehensive survey of investment in biotechnology within the United States. **The levels of U.S. investment in biotechnology presented in this report are informed estimates.** The reader is best served, however, by looking beyond the numbers and recognizing the enormity and diversity of efforts underway within the United States to support research in biotechnology and to promote its application. **Because of the uncertainties in the estimates, reliance on the numbers alone obscures the full picture.**

Numerous issues, other than the level and type of resources invested, direct and affect biotechnology research and development. These factors include the structure of research relationships, quality and availability of personnel, effects of regulations and controls, intellectual property law, and export and trade policy. While many of those issues are discussed within the context of this report, the reader is referred to other reports in the series **New Developments in Biotechnology**. They are *Ownership of Human Tissues and Cells* (7), *Public Perceptions of Biotechnology* (9), *Field Testing of Engineered Organisms: Genetic and Ecological Issues* (6), and *Patenting Life* (8).

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Chapter 3

Federal Funding of Biotechnology Research and Development

"The Administration's R&D budget, like all budgets, must not be viewed in isolation. Budgets are 'carved out' in an environment that is influenced by external pressures and impacts, as well as internal constraints."

Don Fuqua
President, Aerospace Industries Association
Apr. 10, 1987

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Chapter 3

Federal Funding of Biotechnology Research and Development

INTRODUCTION

Historically, the United States, both in absolute dollar amounts and as a percentage of its research budget, has had the largest commitment to basic research in biological sciences worldwide. The vast majority of Federal research support in the biological sciences goes to university scientists conducting basic research, whereas applied research and development (R&D) has always been considered the responsibility of industry. In 1984, OTA suggested that this division of responsibility has contributed to a widening scientific gap between purely basic research funded by the Federal Government and relatively short-term, product-specific applied research funded by private industry. Lack of research dollars for applied fields, such as bioprocess engineering and applied microbiology (generic applied research), was predicted to create a bottleneck in this country's efforts to commercialize biotechnology (6).

There is no hard evidence that this has occurred. Anecdotal evidence, however, suggests that some critical areas of generic applied research in biotechnology remain underfunded because Federal research agencies consider them too applied and industry considers them too basic. As the technologies are integrated into the innovative processes of various industrial sectors, research needs will differ depending on the sector and its state of advancement. There appears to be broad consensus that Federal funding of both basic and applied research has been and will continue to be critical to the U.S. competitive position in biotechnology.

This chapter catalogues the extent to which Federal agencies are funding research in biotechnology-related areas.[1] It does not, however, attempt to evaluate the effect of Federal funding patterns on the U.S. competitive position in biotechnology. In a previous report, OTA described the difficulties of measuring returns from investment in research (9). The data presented in this report provide a foundation from which a careful analysis of existing strengths and weaknesses in the U.S. biotechnology research infrastructure can be derived—the first step in assessing the U.S. competitive position in biotechnology.

Twelve Federal agencies and one cross-agency program (the Small Business Innovation Research Program) have expended substantial funds for biotechnology R&D in recent years. Basic research is the primary mission of several of these agencies, such as the National Institutes of Health (NIH) and the National Science Foundation (NSF). The National Aeronautics and Space Administration (NASA), the Department of Energy (DOE), and the National Oceanic and Atmospheric Administration (NOAA) have large technological development programs but are also substantial supporters of basic research, including biotechnology. Other agencies with diverse missions, such as the Department of Defense (DoD) and the U.S. Department of Agriculture (USDA), fund large numbers of R&D projects related to biotechnology. In addition, agencies with substantial regulatory functions, such as the Food and Drug Administration (FDA) and the U.S. Environmental Protection Agency (EPA), fund research relevant to their regulatory and scientific missions. Finally, agencies traditionally viewed as service oriented, such as the Veterans' Administration (VA), the National Bureau of Standards (NBS), and the Agency for International Development (AID), fund biotechnology research relevant to their service roles.

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[1] The biotechnology funding data presented in this chapter covers fiscal years 1985, 1986, and 1987. All of the data available from the agencies by March, 1988 is included here. Fiscal year 1988 appropriations to the funding agencies, although available, were not included in this report because it was not known how they would be distributed to biotechnology research projects. In certain instances, fiscal year 1988 appropriations to certain agencies are mentioned if biotechnology R&D funded by a particular agency appeared to be affected substantially.

In September 1986, OTA held a workshop on "Public Funding of Biotechnology Research and Training" (8). Representatives from Federal agencies funding biotechnology research and training were invited to present an overview of their agencies' activities. Participants were encouraged to discuss the substance of the research and to be clear about the definition of biotechnology being used to determine spending levels. Chapter 8 addresses the Federal role in supporting training of biotechnology personnel.

Discussions during the 1986 workshop revealed the following points:

- The diversity of work underway using these technologies is remarkable, ranging from the most basic to the most applied. The tools developed through biotechnology have been fully integrated into both basic and applied work, making fiscal isolation of "biotechnology-related" work an arduous task. Because biotechnology draws from established fields such as biology and engineering, it is usually not separately identified in an agency's budget.
- Agencies define biotechnology differently. How an agency defines biotechnology greatly affects the estimate of its investment in the technology. This precludes any direct comparison of spending across agencies and makes summing up a questionable task. For example, EPA's definition of biotechnology is rather narrow compared to the definition used by NIH. Some agencies were able to provide spending figures under two definitions of biotechnology—one narrow and one broad.

This chapter presents an agency-by-agency overview of Federal investment in biotechnology R&D. The definition used by each agency for accounting purposes is presented for clarification. Most agencies provided actual spending figures for fiscal years 1985, 1986, and 1987, although some were unable to account for biotechnology spending, particularly in fiscal year 1985 (see table 3-1).

Table 3-1.—Federal Support for Biotechnology Research, 1985-87 (current dollars in thousands)

Agency	FY 1985	FY 1986	FY 1987
National Institutes of Health:			
Basic	1,208,229	1,202,094	1,388,337
Applied	638,916	678,003	887,614
Total	1,847,145	1,880,097	2,275,951
Department of Defense:			
Basic	44,100	51,600	60,800
Applied	48,500	49,000	58,000
Total	92,600	100,600	118,800
National Science Foundation	81,570	84,072	93,800
Department of Energy:			
Basic	45,500	45,000	50,100
Applied	9,600	10,900	11,300
Total	55,100	55,900	61,400
USDA Cooperative State Research Service	48,000	46,000	49,000
USDA Agricultural Research Service	24,500	27,000	35,000
Agency for International Development:			
Broad definition	NA*	46,854	43,756
Narrow definition	NA	14,332	6,082
National Aeronautics and Space Administration	NA	6,400	7,200
Veterans Administration	5,400	6,365	9,400
Environmental Protection Agency	3,000	3,400	5,666
National Bureau of Standards	850	3,300	3,300
Food and Drug Administration	3,000	4,700	5,800
National Oceanic and Atmospheric Administration	2,144	2,215	2,680
Small Business Innovation Research**	12,033	12,000	NA

*NA: Not available.

**SBIR dollars are a part of the total spending reported by the above agencies. They should not be added on to total spending.

SOURCE: Office of Technology Assessment, 1988.

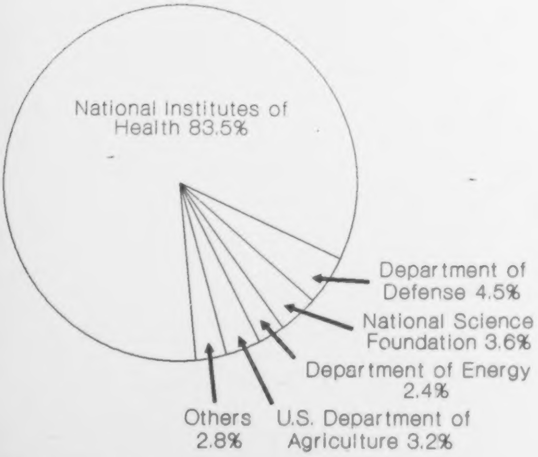
In some cases, estimates were provided for 1988. **In current dollars, the total Federal spending for biotechnology R&D was in the range of $2.16 billion in fiscal year 1985, $2.28 billion in fiscal year 1986, and approximately $2.72 billion in fiscal year 1987.**

NATIONAL INSTITUTES OF HEALTH

Biotechnology is the application of biological systems and organisms to technical and industrial processes. The technologies employed in this area include: classical genetic selection and/or breeding for purposes such as developing baker's yeast, conventional fermentation, and vaccine development; the direct in vitro modification of genetic material, e.g., recombinant DNA, or gene splicing, and other novel techniques for modifying genetic material of living organisms, e.g., cell fusion and hybridoma technology.

The bulk of support for basic biomedical research and training crucial to the development of biotechnology has come from NIH, the government's largest nonmilitary research agency (see figure 3-1). NIH promotes research in two categories crucial to the development of biotechnology: basic research directly related to or using the new techniques that comprise biotechnology, and a larger science base of free-ranging research underlying biotechnology. NIH reported that $2.27 billion (38 percent of the total agency R&D budget) was spent in these two areas in fiscal year 1987. Every institute and research division maintains activities in these areas although there are no designated biotechnology programs. The proportion of funds spent in the two categories varies across institutes, with the most concerted efforts in biotechnology being expended by the National Cancer Institute and the National Institute of General Medical Sciences (see table 3-2 for total expenditures in biotechnology by each Institute, 1983-87).

Figure 3-1.-Federal Support for Biotechnology R&D



SOURCE: Office of Technology Assessment, 1988.

Basic research *directly* related to or using the new biotechnology includes manipulating genomes, cloning DNA, using special techniques to isolate, detect and characterize DNA, creating hybridomas and producing monoclonal antibodies, and using computer methods to analyze DNA and protein sequences and to design new biopolymers. In fiscal year 1987, NIH support for research and training in this category totaled $888 million, up $210 million over 1986 (see ch. 8 for further discussion of NIH support for training).

Basic research *underlying* the new biotechnology includes undifferentiated free-ranging investigations in genetics, molecular biology (investigations of the genetics of organisms, studies at the molecular level of gene replication and regulation), cell biology (examination at the cellular and organ level of development, growth, and senescence), and immunology (analysis of the structure and function of the immune system). Support for research and training in these areas was estimated at $1.39 billion in fiscal year 1987, $0.19 billion over 1986.

Data pertaining to biotechnology research funding are catalogued by NIH on the basis of grant applications or progress reports and indexed by key words. **Budget figures provided are the total costs associated with the awards, including direct and indirect costs, and are not re-**

Table 3-2.—Funding of Biotechnology by Each Institute of the National Institutes of Health: 1983-87

	Year (dollars in thousands)				
Institute*	1983 actual	1984 actual	1985 actual	1986 actual	1987 actual
NCI	335,661	379,737	561,325	559,281	645,588
NHLBI	128,098	154,783	145,215	150,226	169,980
NIDR	13,743	14,170	20,802	21,579	22,003
NIDDK	198,863	224,237	161,354	163,300	246,660
NINCDS	105,212	123,652	142,413	149,758	158,989
NIAID	206,465	221,204	224,828	229,300	297,003
NIGMS	246,421	280,311	282,169	308,775	356,100
NICHD	95,928	108,065	123,673	122,837	161,215
NEI	22,080	28,792	35,225	33,780	37,695
NIEHS	10,941	10,918	13,438	13,714	14,556
NIA	6,222	9,134	13,912	14,775	20,328
NIAMS	—	—	40,757	29,700	48,903
DRR	66,738	87,222	82,034	82,972	96,181
NLM	—	—	—	100	750
Total	1,436,372	1,642,225	1,847,145	1,880,097	2,275,951

*Institute abbreviations refer, in order, to the following: National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute of Dental Research; National Institute of Diabetes and Digestive and Kidney Disease; National Institute of Neurological and Communicative Disorders and Stroke; National Institute of Allergy and Infectious Diseases; National Institute of General Medical Sciences; National Institute of Child Health and Human Development; National Eye Institute; National Institute of Environmental Health Sciences; National Institute on Aging; National Institute of Arthritis, Musculoskeletal and Skin Diseases; Division of Research Resources; National Library of Medicine.

SOURCE: National Institutes of Health, 1988.

lated to the proportion of recombinant DNA research in the total research effort. Thus, some overestimation of the amount going directly to research probably occurs.

In recent years, there has been increasing pressure from the White House and others for NIH to expand its biotechnology support (1,11). NIH maintains that it best supports the scientific base necessary for biotechnology by approving the best basic research proposals submitted to the Institutes for funding. At a 1985 meeting of the NIH director's advisory committee, representatives of some of the smaller biotechnology companies argued for funding by NIH of more generic applied research, those areas requiring intensive capital and posing high risk, such as bioprocessing technologies. They also suggested that NIH promote "intellectual support" for biotechnology companies, allowing NIH scientists to consult with industry, a policy already in the process of change at the time of the meeting.

In 1987, an NIH committee began drafting guidelines that will give companies unprecedented access to NIH resources. These guidelines are in response to the Technology Transfer Act of 1986 (Public Law 99-502), which requires Federal laboratories and their scientists to share their work with industry. Under the guidelines, companies will be guaranteed exclusive licensing rights to the fruits of any research undertaken with a government laboratory. In addition, NIH scientists will be encouraged to seek commercial applications for their work through a system of incentives that includes a share of the royalties gained from product development. The opening of NIH laboratory doors offers great promise to commercial biotechnology, which is so reliant on research funded by NIH and research conducted by NIH scientists (2).

Other important resources for biotechnology firms supported by NIH are the Human Mutant Cell Repository, a cell bank in Camden, NJ, and GenBank®, the nucleic acid sequence data bank, which is also supported by DOE. BIONET is a resource for providing analytical services regarding DNA and protein sequences.

NATIONAL SCIENCE FOUNDATION

Work categorized as research related to biotechnology includes activities in fundamental genetics, cell physiology, cell culture biology, basic biochemistry and enzymology, and bioprocessing engineering, which are generally regarded as being directly related to the further development of biotechnology.

The National Science Foundation has as its mission the support of basic research in colleges and universities in the United States. The NSF budget accounted for about 8 percent ($1.5 billion) of the fiscal year 1987 Federal nondefense budget for R&D. Approximately 94 percent of the NSF budget goes to basic research, with only 6 percent being awarded for applied research. In 1985, NSF made its first awards in its Engineering Research Centers program, established to facilitate technology transfer and multidisciplinary research. One of the first six centers is the Biotechnology Process Engineering Center at the Massachusetts Institute of Technology, which received start-up funds of $2 million from NSF and $150,000 from the National Institute of General Medical Sciences and the National Cancer Institute (both of NIH) in 1985 to investigate engineering technologies for bioprocessing (see box 3-A for further discussion).

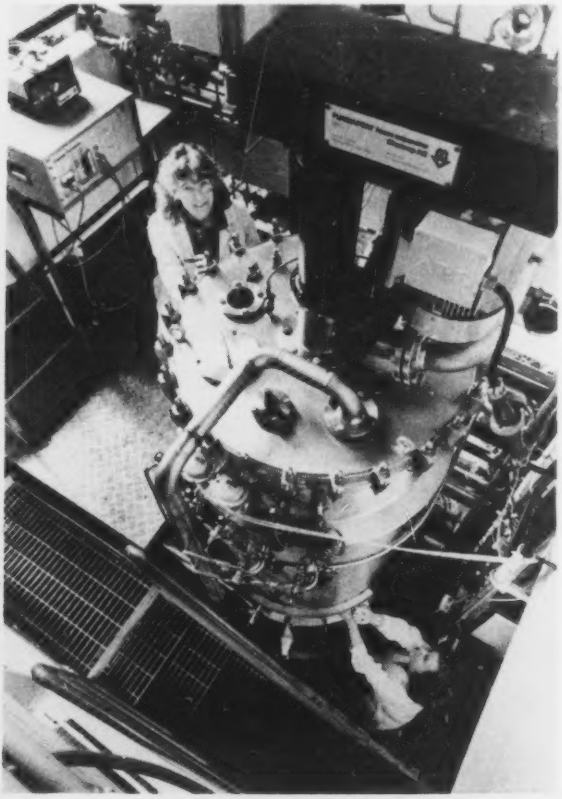


Photo credit: Marvin Lewiton

Undergraduate students working with a 1,500-liter fermenter in MIT's Bioseparations Research Laboratory, supported in part by the National Institutes of Health and the National Science Foundation.

NSF reports that it funded 1,712 biotechnology projects at $84 million in fiscal year 1986. Expenditures for biotechnology R&D in fiscal year 1987 stand at $93.8 million. NSF has requested $108.5 million for biotechnology research in its fiscal year 1988 budget.

NSF determines its biotechnology spending via a new data collection system implemented by an Office of Biotechnology Coordination at NSF. Program officers are required by NSF to judge all new awards for biotechnology relatedness on a subjective scale from none to all by one-third increments. NSF specifies a category of work as related to biotechnology if it includes research activities in fundamental genetics, cell physiology, cell culture biology, basic biochemistry and enzymology, and bioprocess engineering. The largest single area in which NSF identifies research related to biotechnology is genetics, both prokaryotic and eukaryotic. The second largest area is regulation of gene expression.

In addition to direct research support, the NSF instrumentation program provides a great deal of research support for instrumentation acquisition; microchemical instrumentation, most commonly used in biotechnology, is a part. Awards in the instrumentation program are not coded for biotechnology relatedness because use is difficult to predict and the awards are usually made to groups of individuals.

The NSF Engineering Directorate has initiated a program to support multidisciplinary groups in applied biotechnology. This program focuses on the application of engineering to the recent advances in molecular biology, genetics, microbiol-

Box 3-A.—The Biotechnology Process Engineering Center at the Massachusetts Institute of Technology

The Biotechnology Process Engineering Center (BPEC) at the Massachusetts Institute of Technology (MIT) was established in 1985. Funding is provided by the National Science Foundation, the National Institutes of Health, MIT, and industry. Contributions by NIH and NSF since 1985 are:

	NIH	NSF
Fiscal year 1985	$150,000	$2,000,000
Fiscal year 1986	$100,000	$3,000,000
Fiscal year 1987	$100,000	$3,295,000

NSF will provide support for the Center for the first 5 years, after which it must be self-sufficient. NIH funds are primarily intended for undergraduate and graduate training.

Scientists at the Center come from five different departments of two schools within MIT. The School of Engineering contributes faculty from the Departments of Chemical Engineering, Electrical Engineering, and Nuclear Engineering. The Departments of Applied Biological Sciences and Biology participate from the School of Science. The Director of the Center reports to the Dean of Engineering and works with university-comprised committees and an Industrial Advisory Board consisting of 11 biotechnology industrialists. An Operating Committee oversees the education and research of the Center as well as the activities of the Center's Industrial Consortium.

The Center provides educational opportunities for both undergraduates and graduates, and training programs for industrialists in courses such as fermentation technology, microbial principles of biotechnology, drug delivery, downstream processing, and modeling, simulation, and optimization. In addition, the Center houses visiting scientists from industry who spend extended periods of time working in the laboratories.

Foremost on the mind of those involved in the Center is the need to generate industrial sponsorship. By 1987, 15 companies had supported 16 projects totaling approximately $1.5 million. Companies can also donate equipment. In 1986, $770,000 worth of equipment was received. Industry donated $2.4 million for the construction of a fermentation and downstream pilot plant located on the MIT campus that became operational in 1986. The pilot plant, a small but impressive facility, will handle biotechnology processes from fermentation to product isolation.

The Center also hopes to attract a degree of financial independence through its Industrial Consortium, which provides a more formal basis for interaction and collaboration between the Center and industry. Members of the consortium pay an annual subscription fee ranging from $2,000 to $20,000 to receive information and services relating to the activities of the Center. By 1987, 50 companies had signed up.

While still in its youth, the BPEC faces impending adulthood when the Federal purse closes in 1990. Critics of the mandated fund-raising strategy are concerned that superb scientists are spending their time on desperate attempts to raise money when they should be conducting research. Others are skeptical about the ability of the Center to raise sufficient funds from an industry that has no money to spare and plenty of other places to spend it. Proponents of the Center assert that it is encouraging university-industry collaboration in an area where critical applied research and development needs exist.

SOURCE: D.I. Wang, "Biotechnology Process Engineering Center," *The Engineering Research Centers: Leaders in Change* (Washington, DC: National Academy Press, 1987). Personal communication, Office of the Director, Biotechnology Process Engineering Center, August 1987.

ogy, cellular physiology, and biochemistry that have made it possible to use living systems to produce a wide range of economically important substances. Up to $500,000 per year will be provided, for up to 5 years, for research teams to advance capability in biotechnology engineering and to provide a training environment for the biotechnologies of the future.

NSF also funds environmental biology pertinent to biotechnology regulation ($3 million in fiscal year 1985 and $1.9 million in fiscal year 1986), and an area called "impact of biotechnology" ($255,500 in fiscal year 1985 and $241,400 in fiscal year 1986). Bioengineering and bioprocessing research funds increased dramatically from $2,891,000 in fiscal year 1985 to $4,330,200 in fiscal year 1986. Cell culture and genetics also received more funds in 1986 than in 1985, but bioelectronics, bioenergetics, and cell fusion received significantly less support in 1986 (see table 3-3 for a breakdown by field of spending in fiscal years 1985 and 1986).

NSF officials had anticipated the emergence of a new class of awards in the near future that will include greater interaction with the States for supporting larger biotechnology centers, a small number of cooperative activities, and a small number of "mini-centers," which are at the university departmental level. Each of these centers would not necessarily be problem oriented, but would stimulate cross-disciplinary research within the biological sciences. As of early 1988, the funding status of these centers was uncertain because the fiscal year 1988 budget for NSF was not at the level that the agency expected.

Table 3-3.—NSF Support of Biotechnology-Related Research in Fiscal Years 1985 and 1986 (dollars in thousands)

Field	1985	1986
Antibodies/antigens	3,774.8	3,631.9
Bioconversion	1,801.8	1,414.3
Bioelectronics	1,640.2	755.1
Bioenergetics	5,514.4	2,778.9
Bioengineering/bioprocessing	2,891.9	4,330.2
Biomembranes	4,317.5	4,754.5
Cell regulators/cell modulators	9,423.7	10,763.1
Cell culture	2,598.7	4,444.3
Cell fusion	446.8	222.2
Chemistry	7,732.5	6,552.2
Environmental biology	3,010.2	1,945.2
Enzyme structure/function	7,099.1	8,608.4
Genetics	26,501.1	30,699.0
Impact of biotechnology	255.5	241.4
Reproduction	2,600.3	2,384.4
Special resources	1,961.7	546.8
Total	**81,570.2**	**84,071.9**

SOURCE: National Science Foundation, 1987.

DEPARTMENT OF DEFENSE

Biotechnology is defined as any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants, or to develop micro-organisms for specific uses. The technologies specifically included in this definition are recombinant DNA, novel bioprocessing techniques, cell fusion technology including hybridomas, and somatic cell genetics.

The Department of Defense supported 69 percent of *total* Federal R&D in fiscal year 1987, with an R&D budget of $40.8 billion. This is its highest share of Federal R&D since 1962.

In 1986, DoD established a steering committee under the Deputy Undersecretary of Defense for Research and Advanced Technology to examine biotechnology policy within the agency. The committee reports that the DoD effort in biotechnology is essentially divided between two branches of the armed forces; the Army, which supports mostly medical biotechnology; and the Navy, which supports mostly nonmedical biotechnology. The Defense Advanced Research Projects Agency (DARPA) and the Air Force also initiated a small investment in nonmedical biotechnology in fiscal year 1986. DoD intends to decrease funding levels in medical biotechnology and increase funds for nonmedical biotechnology over the next several years.

DoD runs a distant second to NIH in Federal funding of biotechnology research, having spent the equivalent of 1/20th the NIH budget for biotechnology in fiscal year 1987. In fiscal year 1985, the DoD spent a total of $92.6 million on biotechnology research ($44.1 million in basic research and $48.5 million in applied research). In fiscal year 1986, $100.6 million was spent ($51.6 million in basic areas and $49 million in applied). In fiscal year 1987, biotechnology funding was $118.8 million ($60.8 million in basic research and $58 million in applied areas). Overall, DoD funding for biotechnology research is almost evenly divided between intramural and extramural programs—$27.5 million for intramural and $21 million for extramural programs in fiscal year 1986. Since fiscal year 1985, funding has shifted slightly toward more extramural research. Eighty-five percent of the extramural research is conducted in universities. Fiscal year 1987 funding include a $3 million one-time carry over of funds from the Defense University Research Initiative Program (DURIP). Proposed funding of biotechnology R&D for fiscal year 1988 shows only slight growth.

Medical biotechnology is primarily directed toward vaccine development and diagnostic methodology. Targeted vaccines are those against militarily relevant diseases, such as Rift Valley Fever and dengue, that are not of public health concern in the United States but occur primarily in third world countries. DoD and NIH cooperate in vaccine research for malaria. The diagnostics efforts focus on use of DNA probes and monoclonal antibodies, which have also been developed by DoD for its chemical-biological defense program to produce methods for pretreatment, antidotes, and enzymes for decontamination. In 1986, the Army Medical Research and Development Command was largely responsible for funding 57 biotechnology projects ($42 million) in the area of chemical-biological warfare (4). In fiscal year 1986, DoD allocated $32 million for basic research and $49 million for applied research in medical biotechnology—a slight increase over the fiscal year 1985 levels ($30.3 million and $48.5 million respectively).

The nonmedical biotechnology programs in DoD are diverse. One of the areas receiving the greatest funding is materials research: biopolymers, fiber, and adhesives and intermediate compounds for use in composites. Other areas are pollution control, biosensors, biocorrosion and biofouling control, compliant coatings, and biomolecular electronics. Research in these areas was supported at a level of $19 million in fiscal year 1986; essentially all of it being basic research. This figure was up from $13.8 million in fiscal year 1985, primarily due to the DURIP where four universities were funded to do interdisciplinary research in biotechnology as it applies to new materials and marine science. Each program receives approximately $2 million a year, with funds decreasing slightly in fiscal year 1988 after the initial equipment capitalization. In fiscal year 1987, DoD allocated an additional $1.5 million for more applied research in these areas.

Under special programs DURIP supports the purchase of some equipment for biotechnology programs. DoD estimates that about $2.1 million was awarded to universities in fiscal year 1985 for instrumentation directly related to biotechnology. About 15 percent of the funds are spent on industry research.

DEPARTMENT OF ENERGY

Biotechnology related research is defined as research information and methodologies that could be used by industrial scientists to develop the products and processes of biotechnology, and includes research needed as the scientific base to develop that information.

Total expenditures for biotechnology R&D in the Department of Energy were over $61 million in fiscal year 1987, or about 1 percent of its total R&D budget. DOE supports both basic and applied research relevant to biotechnology. Applied research is supported under the Assistant Secretary for Conservation and Renewable Energy and the Assistant Secretary for Fossil Energy. These programs serve DOE's mission of developing a variety of energy resources in an environmentally sound way. Historically, DOE has been involved in research on the medical effects of radiation because of its mandate to oversee atomic energy. Expertise in this area has expanded to other areas of human genetics, plant biology, and biomass resources.

Under the applied research programs of Conservation and Renewable Energy, renewable biomass resources, such as woody and herbaceous crops, are being developed. Projects include species screening, plant breeding, and tissue culture studies ($3.5 million in fiscal year 1987). Other studies include the conversion of biomass to fuel ethanol. Under a biocatalysis project, bioreactors are being studied as a way to produce specialty chemicals ($5.9 million in fiscal year 1987). Biotechnology research in fossil energy includes coal cleaning, liquefaction and gasification, fuel gas upgrading, and techniques to enhance oil recovery from wells. Funding in this area in fiscal year 1987 was an estimated $1.9 million, down from $2.8 million in fiscal year 1986. Thus, the total applied research budget in biotechnology-related areas in fiscal year 1987 is estimated at $11.3 million (see table 3-4).

Research that is basic and relevant to biotechnology is supported by the Office of Basic Energy Research (OBER) and the Office of Health and Environmental Research (OHER). Total support for basic research relevant to biotechnology totaled $50.1 million in fiscal year 1987. In OBER, studies are conducted in plant sciences, quite extensively in bioenergetics, photosynthesis, and control of plant growth and development. Microbial research is conducted dealing with mechanisms of lignocellulose degradation, fermentation, and microbe interactions. In fiscal year 1987, $16.5 million was spent on biotechnology-relevant research in that Office, up from $12 million in fiscal year 1986. Thirty-three percent of the research is conducted intramurally.

OHER has programs in molecular and cellular biology; molecular genetics, cytogenetics, and mouse genetics; structural and analytical studies of macromolecules; and physical ecology. Much of the biotechnology work in OHER is aimed at explaining the molecular basis of mutagenesis and gene expression and the structure of nucleic acids and proteins. The fiscal year 1987 budget for biotechnology in OHER was $33.6 million, modestly increased over fiscal year 1986. Eighty-five percent of the biotechnology-related research is conducted intramurally.

Table 3-4.—DOE Support of Biotechnology R&D, Fiscal Years 1985-87 (dollars in millions)

	1985	1986	1987
Basic research:			
Office of Health and Environmental Research	33.1	33.0	33.6
Office of Basic Energy Research	12.4	12.0	16.5
Subtotal	45.5	45.0	50.1
Applied research:			
Biomass Energy Technology Division	5.6	5.5	5.9
Energy Conservation and Utilization Technologies	2.0	2.6	3.5
Fossil Energy	2.0	2.8	1.9
Subtotal	9.6	10.9	11.3
Total	**55.1**	**55.9**	**61.4**

SOURCE: Department of Energy, 1987.

DOE labs have historically been interested in the human genome, primarily for the purpose of developing techniques that would allow measurements of mutation rates in human populations. In 1986, OHER held a conference, hosted by DOE's Los Alamos National Laboratory, to discuss the feasibility of undertaking sequencing of the human genome. Los Alamos, together with Lawrence Livermore National Laboratory has been involved in the National Laboratory Gene Library Project, an effort to construct a chromosome-specific gene library from isolated human chromosomes.

DOE has proposed mapping the entire complement of human chromosomes known as the human genome—a massive effort ultimately requiring the order of each nucleotide along the DNA in each chromosome to be determined. There has been considerable debate over the extent to which such an effort should be undertaken by the Federal Government and over which agency should coordinate the effort. A subcommittee of the Health and Environmental Advisory Committee (HERAC) of OHER strongly urged that DOE commit a large, multi-year, multidisciplinary undertaking to make a complete physical map of the human genome (10). In February 1988, a National Research Council report urged funding a project to map the entire human genome, but did not specify which agency should lead such an initiative (3). Funding for the DOE initiative in mapping the human genome began in fiscal year 1987, with $4.7 million going to 10 projects at 3 national laboratories and Harvard and Columbia Universities. These projects are aimed at improving existing methods for mapping and sequencing DNA, devising advanced computer analysis methods, and employing automation and robotics to generate new tools for molecular biologists. OTA has published an assessment of issues relating to a human genome mapping initiative (7).

Biotechnology research is also conducted at other DOE labs, such as the Ames Laboratory, Argonne National Laboratory, the Savannah River Laboratory, Brookhaven National Laboratory, Idaho National Engineering Laboratory, Oak Ridge National Laboratory, Pacific Northwest Laboratory, and Lawrence Berkeley Laboratory. These programs are funded primarily out of OEHR's intramural program.

U.S. DEPARTMENT OF AGRICULTURE

Because of the size and complexity of the USDA, programs in biotechnology research and training have been examined in the two major agencies responsible for R&D within the Department—the Cooperative State Research Service (CSRS) and the Agricultural Research Service (ARS). These two agencies differ greatly in both mission and budget. In addition, they define biotechnology differently. Combined, they report spending $73 million on biotechnology research and development in fiscal year 1986. The combined budget increased to $84 million in fiscal year 1987 but will fall to $82 million in fiscal year 1988. CSRS and ARS have been examined separately in this report. Chapter 10 presents a more thorough discussion of U.S. investment in plant agriculture as related to biotechnology.

Cooperative State Research Service

> Biotechnology refers to the improved or modified organism, microbe, plant, or animal, and 'new research techniques' or 'technology' refers to contemporary 'tools' available to scientists for the purpose of biotechnology development.

CSRS is the USDA's liaison to the State university system for the conduct of agricultural research. Of all Federal agencies, CSRS handles the most diverse types of research funding, including formula funds, such as the Hatch Act (1862 Universities), MacIntire-Stennis Cooperative Forestry funds, Evans-Allen funds (1890 Colleges and Tuskegee University), and the Animal Health and Disease Section 1433 funds. The States provide research funds on a matching basis, which now exceed the requirement by about three-fold. Of the total State Agricultural Experiment Station (SAES) research funding, Federal formula funds average 19 percent, State funds over 60 percent, and all other funds (private, Federal grants, etc.) about 20 percent. In addition, CSRS handles the Special Research Grant Program, Competitive Research Grants Program, and USDA Higher Education Fellowships. There are biotechnology programs in all of these funding categories. The diversity of funding mechanisms complicates efforts at developing a central data management system to track all research being done in biotechnology.

The biotechnology research funding from CSRS for fiscal year 1987 totaled $49 million and supported nearly 2,000 individual projects. This is up from $46 million in fiscal year 1986. Funding for biotechnology in 1985, however, was more than double that from the previous year. This was a result of a congressional appropriation of $20 million awarded to the Competitive Grants program for research targeted to agricultural biotechnology.

Research projects in biotechnology include areas using techniques such as tissue culture where specific selection and directed mutagenesis has been used, drug development through use of monoclonal antibodies, DNA probes, DNA sequencing, and protein sequencing. Six hundred projects are being supported in an area labeled "fringe biotechnology," which includes categories such as tissue culture for plant propagation purposes, isozyme isolation for speciation, classical serological work for relationships or for identification, and metabolic studies. Eleven projects being funded are examining the economic and social effects of biotechnology.

The $49 million within CSRS is divided as follows within each funding category: Hatch Act, $11.6 million; MacIntire-Stennis Cooperative Forestry, $231,000; 1890 Colleges and Tuskegee University, $210,000; Special Research Grants, $4 million; Competitive Research Grants, $28.6 million; and Animal Health and Disease, $514,000. The Forestry Competitive Research Grant Program administered by CSRS has $1.7 million for biotechnology and is included in the preceding total. The preceding totals do not include biotechnology research supported by State funding.

Agricultural Research Service

> Biotechnology includes projects that use techniques such as gene cloning in micro-organisms, nucleic acid hybridization, biological and biochemical synthesis of nucleic acids and proteins, use of monoclonal antibodies, affinity column separation of antigens, use of immobilized enzymes and cells, protoplast fusion, regeneration of plants from tissue culture, transfer of embryos, gene mapping, and synthesis of peptide neurohormones.

As its name implies, ARS is the primary research agency within the USDA. It is the in-house agency of USDA on intramural research programs, although it does spend about $20 million a year on specific cooperative agreements. ARS conducts research for specific user groups within the USDA, such as the Animal and Plant Health Inspection Service, Food Safety Inspection Service, and Soil Conservation Service. ARS reports that it is applying the new technologies, particularly the advances in molecular biology, to study and understand fundamental biological processes and to modify and regulate these processes for the solution of agricultural problems. ARS does not consider biotechnology as a discipline or area of research. Thus, resources are allocated to specific high priority problems, and biotechnology techniques or methodologies are used in research projects throughout much of the total program.

In fiscal year 1986, ARS projects using biotechnology techniques totaled about $27 million. These projects involved about 200 scientists who use biotechnology techniques. By the end of 1987 these totals increased to about $35 million and about 350 scientists.

DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

> Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services.

For the past several years, the National Sea Grant College Program of NOAA has invested a small but significant share of its budget to research that will aid in the development of marine biotechnology. Research on marine natural products includes fundamental chemical and biological studies directed toward discovering novel biochemicals whose properties make them of potential use in medicine, medical research, and agricultural and chemical studies directed toward the development of industrial chemicals and materials. In fiscal year 1985, 56 projects in the categories listed below were supported with $2,144,000 in Federal funds and $1,361,000 in matching funds. This accounted for roughly 5.5 percent of the Sea Grant Budget. In fiscal year 1986, total NOAA spending on biotechnology was $2,215,000 for 55 projects. This figure was matched by an additional $1,702,000. In fiscal year 1987, NOAA spending on biotechnology was at $2,680,000 for 66 projects, and matched by an additional $1,789,000.

There are four categories of research: biochemistry and pharmacology (up from $865,000 in fiscal year 1986 to $916,000 in fiscal year 1987); genetic engineering (up from $624,000 in fiscal year 1986 to $778,000 in fiscal year 1987); biochemical engineering (down from $581,000 in 1985 to $393,000 in 1987); and microbiology and botany (up from $342,000 in 1986 to $593,000 in fiscal year 1987) (see table 3-5). All Sea Grant research is conducted extramurally.

Research in biochemistry and pharmacology—the fields receiving the most funds—is directed toward isolation, identification, and biological evaluation of novel marine substances of potential use in medicine or industry. Two new anticancer compounds, for example, were isolated and are under further evaluation by the National Cancer Institute. Other research areas focus on manipulation of the genetic complement of animals or micro-organisms to produce useful diagnostic or quality control reagents, control diseases of marine organisms, process waste materials, and enhance the growth and competence of aquacultured species.

Projects categorized under "biochemical engineering" concern the production of materials and development of processes potentially useful in industry. For example, academic scientists interested in the nutritional role of vitamin B and its analogues—the cobalamins—in the biological processes of the ocean have isolated from marine animals novel proteins with an extraordinary affinity for vitamin B. Subsequent studies showed the proteins to be cheaper and more specific reagents for determining vitamin B than current reagents used in clinical chemistry. Their commercialization, which is in the early collaborative stages with

Table 3-5.—NOAA Funding for Sea Grant Projects in Biotechnology in Fiscal Years 1978 to 1987 (dollars in thousands)

Category	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
Biochemistry and pharmacology	382	465	440	402	525	440	671	820	865	916
Genetic engineering	—	—	—	100[a]	266	419	487	537	624	778
Biochemical engineering and industrial chemicals	206	246	349	285	454	515	540	581	384	393
Microbiology and phycology	—	—	—	50[a]	100[a]	284	248	206	342	593
Totals	588	711	789	837	1,345	1,658	1,946	2,144	2,215	2,680

[a] Estimate

SOURCE: U.S. Department of Commerce, National Oceanic and Atmospheric Administration, 1988.

industry, is expected to be successful and to increase the sophistication of studying diseases such as pernicious anemia and certain mental disorders.

National Bureau of Standards

> Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services.

The Senate Committee on Commerce, Science and Transportation in its report on the authorization of the National Bureau of Standards (NBS) for fiscal year 1985, directed NBS to prepare a plan on a national effort in measurements and standards for biotechnology. The plan recognized that commercialization of biotechnology will be measurement intensive with an estimated cost of up to 25 percent added to the products of biotechnology for measurement. Measurements are made at each stage in the development of biotechnology products, from the original design of production processes, through the acquisition of raw materials, to the ultimate consumption of products in the marketplace. These measurements are primarily chemical and physical in nature.

The Biotechnology Program at NBS is a new program, created to develop measurement methods and standards to advance the commercialization of biotechnology in the United States. The main focuses of the research are:

- development and standardization of techniques needed to achieve homogeneity in protein samples;
- assessment of purity of samples produced by biotechnological methods including primary protein structure determination; and
- aiding industry on standards problems related to the scale-up and automation necessary to get biotechnology from the laboratory to the commercial marketplace. This includes research in catalysis, analytical and process measurements, and separation technology.

In fiscal year 1985, NBS spent $850,000 to determine its capabilities in advance measurement in biotechnology, setting of standards, and developing reference data. In fiscal year 1986, $1.9 million was allocated from the NBS Director's competence fund and $1.4 million was allocated for the new biotechnology initiative by congressional appropriation; $411,600 of this was spent on equipment. Thus, a total of $3.3 million was allocated in fiscal year 1986 for biotechnology, approximately 2 percent of the total NBS budget. The fiscal year 1987 budget for biotechnology remained at $3.3 million.

Approximately 40 percent of the research is basic and 60 percent is generic applied. An example of generic applied research is two-dimensional electrophoresis, where research is needed to improve technique reproducibility. Another example is research on the dynamic properties of fluids, an area critical to bioengineering.

One of the most ambitious new biotechnology projects at NBS is a joint venture with the University of Maryland in Montgomery County, MD. This venture, called the Center for Advanced Research in Biotechnology (CARB), will combine interdisciplinary, biotechnology-related resources from academia, industry, and government in an organization that will serve as a national resource for biotechnology-related measurement research and services (see ch. 9). There are plans to involve more universities in this joint venture.

A committee within NBS has been established to define standards that will be needed in biotechnology. Examples are characterization and identification of biomolecules, bioengineering processing and controls, and improved x-ray and neutron data collection.

NBS anticipates a growing need for the development of clinical standards for testing new biotechnology products, such as standards that are used to calibrate scientific instruments and to validate and evaluate data. Work being done to provide data needed in bioengineering is mainly focused on fermenters, establishing equilibrium constants, diffusion coefficients, and mass transport coefficients needed to build from the laboratory to the industrial bioreactor. The Center for Chemical Engineering at NBS is developing sensors that can be used in connection with bioreactors.

AGENCY FOR INTERNATIONAL DEVELOPMENT

Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses.

AID, an agency of the State Department, is the foreign assistance arm of the U.S. Government and is not, per se, a research agency. The Agency's mandate is to work with developing countries in their efforts to meet basic human needs—to overcome the problems of hunger, illiteracy, disease, and early death. Technology development and transfer, including biotechnology, is one of the basic components in the Agency's strategy to achieve its goal. Given the nature of this goal, the research supported by AID is clearly directed to the development of specific products or systems that will be useful in improving human health conditions, agricultural production, and rural development in the developing world. AID supports projects in the United States and overseas. In general, AID finances research that is expected to produce usable results within 3 to 5 years.

The overall research portfolio is comprised of projects supported from several offices within AID, and reflect the Agency's organization. AID is divided into central and regional bureaus and independent offices. Regional bureaus focus on the needs of a specific geographic region and serve as the Washington coordinating arm of the field activities conducted by AID missions. Central bureaus address agency-wide questions, e.g., private enterprise. The central Bureau for Science and Technology provides technical assistance for the entire agency, and supports and initiates worldwide programs in science and technology. This bureau also coordinates AID's support of the 13 International Agricultural Research Centers. An additional locus of research activity was established in 1980, with the creation of the Office of the Science Advisor. The purpose of this office is specifically to encourage an innovative and collaborative approach to development research, technology transfer, and related capacity building.

AID tries to enter established research programs and applies its funds to direct some of the established work toward a particular problem that is currently underfunded. For example, a project to develop a vaccine to rinderpest—a serious prob-

Table 3-6.—AID Funds for Biotechnology in Fiscal Years 1986 and 1987

(dollars in thousands)

	Broad definition		Narrow definition	
Administrative unit	1986	1987	1986	1987
Regional Bureaus/Country Missions				
Thailand	4,400	2,000	1,100	—
India:				
Agricultural	1,617	1,500	404	—
Health	4,600	5,413	1,150	—
Latin America/Caribbean	—	45	—	—
Bureau for Science and Technology				
Agriculture:				
Plants	2,662	1,460	663	—
Animals	1,135	714	898	—
International Agriculture Research Centers	10,000	5,000	2,000	2,000
Health:				
Vaccines	9,000	9,400	3,000	—
Diagnostics	800	2,400	400	—
Therapeutics	—	4,300	—	—
Vectors	1,700	—	200	—
Population:				
Contraceptive immunology	918	1,000	918	250
Office of the Science Advisor:				
Health	2,996	3,099	1,032	1,215
Agriculture	7,026	7,425	2,567	2,617
Totals	**46,854**	**43,756**	**14,332**	**6,082**

SOURCE: U.S. Agency for International Development, 1987.

lem in Africa—is being conducted by scientists at the University of California at Davis, where research was underway prior to AID involvement. AID has supplemented the effort through additional funds and is supporting postdoctoral training for two African scientists so that they can continue research in their native country. In another example, AID has piggybacked onto a Colorado State University (CSU) research project that is directed toward increasing the genetic diversity of rice, sorghum, millet, and other crops heavily used in underdeveloped countries. Researchers from developing countries are supported for a 6-month training program at CSU.

AID provided OTA with two sets of budgetary figures for biotechnology activities in fiscal years 1986 and 1987 (see table 3-6). One set adopts the broader OTA definition and arrives at a total figure of $46.8 million in 1986, and $43.7 million in 1987 (about 3 percent of the total AID budget); the second set narrows the definition to focus specifically on recombinant DNA, cell fusion, and novel bioprocessing techniques, arriving at a total figure of $14.3 million in 1986 and $6 million in 1987 (1 percent of the total AID budget).

U.S. ENVIRONMENTAL PROTECTION AGENCY

Biotechnology is defined generally as the use of living organisms to produce products beneficial to mankind. It is the application of biological organisms to technical and industrial processes. It involves the use of 'novel' microbes, which have been altered or manipulated by humans through techniques of genetic engineering.

The U.S. Environmental Protection Agency (EPA) is primarily a regulatory agency, although research programs providing a scientific basis for regulatory activities accounted for nearly 25 percent ($320 million) of the agency's total budget in fiscal year 1985. Roughly 1 percent of the R&D budget ($3 million) was devoted to biotechnology research and biotechnology risk assessment. The majority of those funds, approximately $2.5 million, was devoted to areas relevant to risk assessment; $500,000 was devoted to product development, most of which is relevant to risk management for deliberate release of genetically engineered organisms. Total spending on biotechnology in fiscal year 1987 increased to nearly $5.7 million from $3 million in 1985 and $3.4 million in 1986.

At EPA, biotechnology research is principally focused on the fate, public health, and environmental effects that might result from the accidental or purposeful release of genetically manipulated organisms into the environment. Officially initiated in 1985, the research program attempts to develop the capabilities for the regulatory programs within EPA to predict and thus avoid unreasonable adverse effects on the environment.

The techniques and knowledge gained through the biotechnology research program are used directly in the risk assessment process required to fulfill the EPA's legislative mandates. Most of the risk assessment work is done at the EPA Corvallis Laboratory in Oregon, which focuses on terrestrial activities, and the Gulf Breeze Laboratory in Florida, focusing primarily on aquatic research and product development. Eighty percent of the program is funded extramurally.

A major need, presently central to research program planning, is predictive risk assessment models for products of manipulated microbes. In conducting its research in this area, EPA actively coordinates and cooperates with industry, public interest groups, academia, and other Federal agencies.

The use of bioengineered organisms to degrade and otherwise mediate hazardous wastes promises great economic reward. EPA policy states that the development of these processes should be the prerogative of the private sector. To build a knowledge base by which to monitor these technologies, EPA is involved in limited studies of genetically engineered microbes for degradation of toxic wastes to better understand potential environmental and health effects as well as the needs for remedial action (see ch. 11). In fiscal year 1986, $589,000 was allocated for these studies; in fiscal year 1987, $531,000. The remainder was spent on research directly related to risk assessment.

VETERANS ADMINISTRATION

The Veterans Administration adopted the OTA definition of biotechnology for the purpose of accounting. Specifically, funding data were provided for projects involving cell fusion, gene splicing, monoclonal antibodies, and recombinant DNA.

During fiscal year 1985, the Veterans Administration (VA) Office of Research and Development tracked a total of 11,355 research projects conducted by 5,808 principal investigators in 143 hospitals. Most VA research concerns clinical medicine ($164 million of a total R&D budget of $184 million in fiscal year 1985). In 1985, of the 11,355 projects, the VA estimates that 100 projects were clearly directed toward the development of biotechnology products or produced information that may later be incorporated into the development of a biotechnology product. These 100 projects were funded at a level of $5.4 million (approximately 2.9 percent of the total R&D budget).

In 1986, the number of projects directly or indirectly related to biotechnology nearly doubled to 196, with support totaling $6.36 million, or approximately 3.5 percent of the total R&D budget for 1986. A total of 266 biotechnology projects were funded in fiscal year 1987, with support totaling $9.40 million, or approximately 4.2 percent of the total R&D budget.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

Space biotechnology includes natural and manipulative processes involving biological materials, such as cells and proteins. The changes that occur in these processes in the reduced gravity environment are dependent on the relationship of the forces involved in the process and in the techniques used.

Biotechnology research at NASA is conducted principally through the Microgravity Science and Applications Program. The purposes of this program are:

- to use the microgravity environment to enhance certain separatory processes for purification of biological materials for therapeutic and diagnostic application to diseases and to solve basic research problems;
- to use the microgravity environment to enhance crystallization of proteins and other macromolecular materials for detailed studies of molecular structure and to enhance production of biocompatible materials; and
- to obtain basic information on the effect of the microgravity environment on certain biological processes in cells, organs, and organisms such as cell secretion, cell-cell interaction, cell growth and differentiation, biorheology, and animal and plant cell manipulations.

Funded at a level of $7.2 million in fiscal year 1987, the program involves investigators from 11 universities, two NASA Centers, one research center, two industrial firms, and two Centers of Excellence. The Centers of Excellence are located at the University City Science Center in Philadelphia ($450,000) and the University of Arizona ($450,000). The Bioprocessing and Pharmaceutical Center in Philadelphia is a consortium of universities looking at separation processes, cell culturing, and cell harvesting. The Center for Separation Science in Arizona also investigates separation processes, primarily in the area of isoelectric focusing.

Of the $7.2 million, NASA spent $1.2 million on university research in separation techniques, cell productivity in reduced gravity, theoretical flow analysis, cell culture and product harvesting in low gravity, and biorheology; $1.9 million on university funding in protein crystal growth and macromolecular crystallography; and $3.1 million in-house at the Marshall Space Flight Center and the Johnson Space Flight Center on many of the preceding areas and flight hardware development.

FOOD AND DRUG ADMINISTRATION

Biotechnology is the application of biological systems and organisms to technical and industrial processes.

The purpose of FDA's research, including biotechnology-related research, is to generate and gather essential scientific information that the agency needs to make regulatory decisions. Under the Federal Food, Drug, and Cosmetics Act and related laws, the FDA is responsible for ensuring that the Nation's pharmaceutical, biological, medical devices, and radiological products are safe and effective and that the food supply is safe and nutritious. To accomplish these activities, FDA uses an institutional research capacity that can fulfill the needs that are unique to its regulatory mission.

Some research, for example, enables FDA to develop quick, accurate, sensitive, and reproducible methods that can be applied in response to public health emergencies (e.g., Tylenol tamperings, *Listeria* contamination of cheese). Other FDA research findings are translated into the development and approval of products critical to public health (e.g., licensure of HIV antibody test kits) or are used to enable FDA to meet long-term regulatory responsibilities (e.g., risk assessment). While most of FDA's research is performed inhouse, a small portion is supported through extramural grants and contracts, such as the Orphan Product development program.

FDA research efforts, including those related to biotechnology, are targeted to these areas:

- product testing;
- scientific review of new product applications;
- identification of hazards;
- development of new or improved physical, biological, toxicological, or chemical tests;
- determination and establishment of standards, and determination of product compliance with those standards; and
- clarification of mechanisms underlying toxicologic and pharmacologic effects.

FDA reported difficulty in assessing accurately the extent to which the agency's research fits the broad category of biotechnology. While many of FDA's research programs may use biotechnology methods, these methods serve as a means to an end—the technology itself is not an endpoint. The FDA spent approximately $3 million in fiscal year 1985 (3.7 percent of the total R&D budget) on research activities that can be considered biotechnology related. This figure rose to $4.7 million in 1986 and $5.8 million in 1987. Most of the funding increase has gone to research in the Center for Drugs and Biologics, involving recombinant DNA or monoclonal antibody methodologies. The research projects are categorized as involving specific pathogens, interferon research, research on antibodies and immunity, and related drug research.

SMALL BUSINESS INNOVATION RESEARCH PROGRAM

Biotechnology is a broad term that includes a number of techniques, such as genetic engineering, protein engineering, processes for making monoclonal antibodies, and other molecular biological techniques; the development of instruments to carry out such techniques is also included in the broad definition of biotechnology R&D.

Approximately $1.1 billion was awarded to small businesses by Small Business Innovation Research (SBIR) programs through fiscal year 1987 (5). The Small Business Development Act of 1982 (Public Law 97-219) established these programs to encourage innovation by requiring Federal agencies to set aside portions of their research funds to small businesses through special research programs. The Act requires Federal agencies that spend more than $100 million annually on extramural research to set aside 1.25 percent (when fully operational) of those funds for an SBIR program. Small businesses submit proposals in response to research topics contained in agencies' solicitation agreements, published at least annually by each participating agency.

Biotechnology companies have done well by the SBIR program. The National Institutes of Health, with the largest civilian research budget, contributes the largest dollar amount to SBIR. NIH awarded 98 of a total of 482 SBIR grants and contracts to 58 biotechnology companies in fiscal year 1986. The awards were worth approximately $5 million.

Biotechnology companies have received a smaller proportion of the total awards from the SBIR programs of the National Science Foundation, the USDA, and the Department of Energy. **In the years 1983-86, 10 percent of the total awards ($36,410,000) made by all SBIR programs have gone to biotechnology and microbiology research in entrepreneurial firms. Three-fourths of those funds came from NIH**. Agencies include SBIR funds in their biotechnology funding figures; thus, the SBIR contribution to biotechnology R&D is subsumed under total Federal spending on biotechnology. SBIR support for biotechnology research surpasses support for information processing, and medical instrumentation, the next runners up.

Recipients of SBIR funds praise the program, stating that it has given them the boost needed to seek commercialization of new products. Public Law 97-219 included a sunset provision and was scheduled to terminate October 1, 1987, but was reauthorized for 5 years—until 1993. SBIR funds are one of the few sources of direct Federal support for applied research and development conducted by small companies, and the SBIR program is widely supported by dedicated biotechnology companies in many business sectors.

SUMMARY AND CONCLUSIONS

Federal support of biotechnology research and development exceeded $2.72 billion in fiscal year 1987, and has not changed substantially in current dollars since 1985. NIH provides by far the most Federal funds for both basic and applied biotechnology research, supplying nearly 84 percent of the Federal Government's biotechnology research dollars. The Department of Defense biotechnology R&D effort consists of an additional 4.5 percent of total spending, and the National Science Foundation funds 3.6 percent. The fact that so many other agencies, including those with missions that are not primarily research, fund work in biotechnology attests to its wide-reaching applications.

Diverse biotechnology applications are supported by most of the Federal agencies. The DoD supports work in materials science and medicine, while NSF funds biotechnology research applications in genetics, bioelectronics, and environmental biology. Some redundancy, a necessary and healthy attribute of the U.S. research infrastructure, also exists across many agencies. In some cases, agencies have cooperated on projects of common interest. Examples in this category are GenBank®, and programs in plant biology and vaccine development.

From the funding data, it appears that Federal agencies are supporting more applied work in biotechnology than was reported to OTA in 1984. Increased attention to application has been most noticeable through the success of the SBIR program in assisting small biotechnology companies. The National Science Foundation hopes to eventually devote additional funds to Engineering Research Centers that focus on biotechnology. NIH, DOE, and DoD also report more funds being dedicated to applied research related to biotechnology. **However, OTA did not request information to determine whether the apparent increase in applied research was due to decisions by the agencies to target this area for increased funds, or to their increased proficiency in accounting for applied work**.

Some caution must be taken in interpreting the OTA totals for Federal funding of biotechnology R&D. The fact that different agencies define biotechnology differently makes it difficult to compare funding across agencies. The difference in definitions reflects the different scientific and political perspectives and varied missions of the agencies. Some agencies, such as NSF and DOE, define biotechnology broadly, in terms that include biotechnology applications typical of the years before the development of recombinant DNA technology. In contrast, agencies such as DoD, the Agricultural Research Service, and the Veterans Administration use definitions similar to the OTA definition of new biotechnology (6) that includes recombinant DNA, cell fusion, and novel bioprocessing techniques. Furthermore, agencies such as NIH and NSF have implemented more efficient mechanisms for cataloging and accounting for research and spending in certain areas, such as biotechnology.

The estimated $2.72 billion spent by Federal agencies in fiscal year 1987 could overshoot or undershoot the actual value, because it is not based on a single definition. These same problems affect biotechnology funding figures submitted by the individual States (ch. 4), or by different companies representing different industries (ch. 5). Nevertheless, totaling the dollars invested in biotechnology R&D by the Federal, State, and private sectors is the only way to compare their relative contributions.

Institutionalization of a government-wide definition of biotechnology could have limited value. Even if a uniform definition were adopted, agencies would still be likely to overcount or undercount, either because they do not have reliable systems for accounting for biotechnology research, or because it is in their institutional interest to do so. **Systematic accounting mechanisms on the part of each of the agencies should be sufficient for budgetary purposes, and given the diversity of agency missions, a cross-agency comparison seems pointless.**

The information contained in this chapter was collected to provide a foundation that future studies can use to address a number of important policy questions pertaining to Federal funding of biotechnology R&D, including:

- Are some categories of research overfunded or underfunded based on the perceived needs of the specific agencies, State and local needs, national needs, and the needs of other nations?
- Are expenditures sufficient to promote the growth of future biotechnology applications?
- Is the research base in biotechnology funded by the Federal Government adequate to maintain or enhance the U.S. competitive position internationally in the various industries affected by biotechnology R&D?
- Is the distribution of Federal funds among the various agencies and their respective missions (e.g., health, agriculture, and defense) appropriate?

Obtaining answers to these questions is beyond the scope of this report. However, the case studies on the U.S. investment in applications of biotechnology to human therapeutics, plant agriculture, and waste management (chs. 9, 10, and 11, respectively) offer a deeper analysis of many of the policy issues relevant to these business sectors, and demonstrate how the factors influencing investment in biotechnology R&D must be considered on an industry-by-industry basis.

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Chapter 4

Biotechnology in the States

"We've got to do something to get this biotechnology applied in Illinois faster than it is in other countries."

Don Holt
Director, University of Illinois
Agricultural Experiment Station

"Biotechnology will change the world, giving us new tools in crop and livestock production and processing. For a $35 million investment, Iowa State University officials are confident we will attract over $120 million in research to Iowa over the next decade."

Governor Terry Branstad
Condition of the State Speech
January 12, 1987

"I don't think the people want the Biotechnology Center investing in the development of small businesses and their research without doing it very carefully."

Gerry Hancock
Former North Carolina State Senator

"Competitiveness may be a new issue to the Federal Government, but it's old news to the States. While the precedents for forward-looking national strategies are few and far between, the 50 State governments have long been laboratories for policy experimentation."

Christopher M. Coburn
Executive Director
Ohio's Thomas Edison Program

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Chapter 4

Biotechnology in the States

INTRODUCTION

In the past 20 years, State governments and local groups have increasingly used investment in high-technology industries as an economic development strategy. High-technology promises clean "sunrise" industries, an improved economy, new jobs, and a strengthened higher educational system.[1] Recently, many of these initiatives have focused on biotechnology. States have different expectations about returns from biotechnology investment, which is reflected in how and where they spend their money. Some States, for example, spend money recruiting faculty at State universities to build a reputation that will then attract businesses into the area. Others direct most of their funds toward small firms, providing incentives and facilities for start-up. Most States pursue a combination of goals. How the States direct their biotechnology efforts depends on their existing industrial, educational, or natural resource base, and their philosophy on the role of State government in fostering small business development. Those States that are successful in nurturing the biotechnology industry rely on strong academic and research programs, a strong, local venture capital pool, and an unusually high level of interaction among researchers, manufacturers, and users.

This chapter examines State investment in biotechnology. In fall 1986, OTA surveyed all 50 States and the territories to determine the extent to which they are investing in new initiatives in biotechnology. OTA found a significant level of interest in biotechnology development at the State level; 33 States have allocated funds for biotechnology through centers of excellence, university initiatives, incubator facilities for new firms, or grants for basic and applied research in biotechnology. While most programs are too young to evaluate their success, their expectations are high.

BIOTECHNOLOGY AND ECONOMIC DEVELOPMENT

Increasingly, State programs to foster economic growth and employment through the promotion of high-technology development surpass those found at the Federal level. As recently as 1980, only 10 States had programs promoting high-technology growth (15). Six years later, at least 43 States had high-technology programs, spending a total of $700 million in 1986 (5). OTA found that 33 of those programs include biotechnology.

In many ways, States are better able to leverage support, influence industry, and affect education than the Federal Government. State governments have traditionally performed key functions of importance to national economic development, such as basic infrastructure maintenance and improvement, basic and higher education, employment training and skills enhancement, financing for export stimulation, and promoting technological innovation. States are critically situated to promote university-industrial linkages that can facilitate the commercialization of research (14).

In most States, the Governor's executive offices for economic planning and development, department of commerce, or department of higher education have served as catalysts for promoting university-industry cooperation as a means for development. These initiatives are usually based on an analysis of the State's existing industrial base, and are undertaken in conjunction with more traditional economic development activities.

Economic development activities in the States seek to create jobs by offering inducements to companies. States compete with each other by targeting attractive industries. What is new about these programs is their emphasis on expanding existing markets and creating new ones by accelerating innovation (8). State governments are attracted to high-technology industry because of the rapid expansion and its presumed potential to create jobs and revitalize distressed regions. States perceive biotechnology as a highly attractive set of industries because of its diversity of application, its dependence on a highly skilled, highly educated work force, its reliance on academe, and the short cycle from discovery to product. High-technology industries are also perceived to have fewer known environmental (and possibly occupational safety) problems than traditional manufacturing industries. This perception has changed, however, as communities face field testing of genetically engineered organisms and the prospect of gene therapy (13).

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[1] For the purposes of this discussion, OTA adopts the Department of Labor definition of "high-technology" industries, as those industries with a ratio of R&D expenditures to net sales at least two times the average for all industries.

The rapid growth of State programs in biotechnology is an extension of previous State efforts to attract high-technology industries. For example, the growth of the microelectronics industry in California and Massachusetts (and the subsequent benefits accrued by those States) sent tempting messages to States dealing with declines in basic industries. Early successes with high-technology development (fostered by strong universities) positioned California and Massachusetts well for growth in biotechnology. Furthermore, previous experience may well have given them the lead they now enjoy in Statewide biotechnology development. Ironically, State government involvement in promoting biotechnology in these two States was minimal until 1985, most likely due to the lack of a need for additional catalysts.

Although California and Massachusetts house the largest percentages of dedicated biotechnology companies (27 and 13 percent of U.S. companies respectively), many other States have shown a keen interest in the development of biotechnology and have undertaken major initiatives to cultivate the industry.

Biotechnology Promotion at the Local Level

Some biotechnology efforts are developing or being initiated at the local level. The Biotechnology Park in Worcester, MA, was initiated and organized by the Worcester Chamber of Commerce, with funding assistance from local sources and the State. The concept of a Biotechnology Center affiliated with the University of California at San Francisco was discussed by the San Francisco Chamber of Commerce and endorsed by then Mayor Dianne Feinstein.

In Texas, the competition for State preeminence in biotechnology has generated local initiatives. The Dallas Biotechnology Task Force, established in 1984, raises money for the Dallas Biomedical Corporation, which will provide interim financing for research projects with commercial potential at the University of Texas Health Science Center in Dallas. Austin is competing with San Antonio to be the Texas center for biotechnology. San Antonio Mayor Henry Cisneros has been promoting biotechnology as a means to economic development and has proposed a 1,500-acre research park to attract biotechnology firms.

Table 4-1.—State Mechanisms for Promoting Biotechnology Development

Policy bodies:
- Governor's task forces, boards, councils, and commissions
- State mission agencies
  - —Commerce/economic development
  - —Higher education
  - —Science and technology offices

Appropriating and granting bodies:
- Legislature
- Nonprofit corporations
- Colleges and universities

Capital:
- Financial capital:
  - —Seed capital funds
  - —Venture capital partnerships
  - —Pension funds
  - —Grants
- Physical capital:
  - —Land use and zoning
  - —Research and science parks
  - —Incubator facilities
  - —Improvements in infrastructure
- Industrial revenue bonds

Management support:
- Business advocacy programs
- Government marketing programs
- Data retrieval and dissemination

Education:
- Kindergarten through grade 12
- Colleges and universities
- Worker training

SOURCE: Office of Technology Assessment, 1988.

Photo credit: Thomas Morrisette, Worcester Area Chamber of Commerce

"One Biotech Park." This 75,000-square-foot structure is the first building completed at the 1 million square foot Massachusetts Biotechnology Research Park located in Worcester, MA. As of March 1988, the building was fully leased.

In Maryland, Montgomery County has donated $9 million worth of facilities and additional millions in land to the Center for Advanced Research in Biotechnology, which is also funded by the University of Maryland and the National Bureau of Standards of the U.S. Department of Commerce. The county hopes to attract more biotechnology firms to its already thriving high-technology corridor. With a high percentage of scientists and engineers per capita and its close proximity to several Federal laboratories and research institutions, the county believes it is well positioned for development of a biotechnology-based industry.

In New York City, Columbia University has planned a $200 million biotechnology research park to be jointly funded by the city, the State, and the university. Four buildings to house academic and commercial research laboratories, office space, and retail outlets are planned. Officials hope that the research park will foster the biotechnology industry in New York City, revitalize a depressed neighborhood, and enhance the university's research capabilities.

Because dedicated biotechnology companies require less physical space than traditional manufacturing industries, cities and counties can offer land and low rent to companies. But cities and counties may be somewhat more limited than the States in what they can offer to attract these industries in a significant way. In contrast, at the State level, diversity of means can promote this industry. Many States can support biotechnology initiatives through appropriations from their legislatures or grants from nonprofit corporations. Support can take the form of financial or physical capital, management assistance, or education. Traditional methods for assisting small businesses, especially those in high-technology areas, are increasingly used to promote biotechnology development. Table 4-1 summarizes the mechanisms OTA found States using to promote commercialization of biotechnology.

OTA SURVEY OF STATE PROGRAMS IN BIOTECHNOLOGY

An OTA survey of State activities in biotechnology conducted in Fall 1986 found that 33 States and Guam directly support biotechnology activities, such as research, training, or development of facilities for research. An additional six States indicated they were conducting feasibility studies or were considering establishing a biotechnology initiative. The OTA survey revealed a wide range in the intensity level of these initiatives and diversity in their implementation. However, all of the States reporting intensified efforts on behalf of biotechnology report doing so in hope of economic development or promotion of academic excellence.

The States differ in their efforts in the following ways:

- the office, agency, or institution primarily responsible for the initiation of the program;
- the level of funding available annually for the support of research, facilities, or training;
- the mechanisms by which funds are raised;
- the base and method of operation for the program;
- the substantive concentration of the programs being funded; and
- the extent to which incentives are offered to attract biotechnology companies.

The types of initiatives States pursue depend, in part, on the influence of these factors. Therefore, the types of initiatives reported varied greatly. Some States are pursuing one path only, others a combination of approaches. The types of initiatives include:

- increased support for biotechnology research and development (R&D) in State universities and by biotechnology companies (33 States),
- programs or funds for biotechnology training at State colleges and universities (23 States),
- financial and technical assistance for biotechnology firms (27 States),
- discrete "Centers" mandated to facilitate communication between universities and industry to achieve technology transfer (28 States), and
- State-supported research parks and incubator facilities specific to biotechnology (6 States).

Table 4-2 displays the types of programs supported by States active in the promotion of biotechnology research and development within their borders.

Table 4-2.—State Activities in Biotechnology Research and Development

State	R&D Support	Training	Incentives for firms
Alabama	–	–	–
Alaska	–	–	–
Arizona	+	–	+
Arkansas	+	–	+
California	+	+	+
Colorado	+	+	+
Connecticut	+	+	+
Delaware	–	–	–
Florida	+	+	+
Georgia	+	+	+
Hawaii	–	–	–
Idaho	+	–	–
Illinois	+	+	+
Indiana	+	–	+
Iowa	+	+	+
Kansas	+	–	+
Kentucky	+	+	–
Louisiana	+	–	–
Maine	–	–	–
Maryland	+	+	+
Massachusetts	+	+	+
Michigan	+	+	+
Minnesota	+	+	+
Mississippi	–	–	–
Missouri	+	–	–
Montana	–	–	+
Nebraska	–	–	–
Nevada	–	–	–
New Hampshire	+	+	–
New Jersey	+	+	+
New Mexico	–	–	–
New York	+	+	+
North Carolina	+	+	+
North Dakota	+	+	–
Ohio	+	+	+
Oklahoma	+	–	–
Oregon	+	+	–
Pennsylvania	+	+	+
Rhode Island	–	–	–
South Carolina	–	–	–
South Dakota	–	–	–
Tennessee	+	+	–
Texas	–	–	–
Utah	+	+	+
Vermont	+	–	+
Virginia	+	–	+
Washington	–	–	+
West Virginia	–	–	+
Wisconsin	+	+	+
Wyoming	–	–	–

SOURCE: Office of Technology Assessment, 1988.

Promotional and Implementation Base of State Biotechnology Programs

The 33 States reporting to OTA about their biotechnology programs represent a variety of approaches to the initiation and promotion of biotechnology. Although university systems play a major role in the design and implementation of biotechnology centers, the initiative for a biotechnology program in some States has come from the Executive Office of the Governor or the State legislature. The programs are often multi-faceted, and can involve direct funding of basic and applied research, allocations for university facilities or equipment, support of faculty salaries, or direct or indirect assistance to biotechnology companies.

Governor's Task Forces or governors with significant interest in high-technology promotion have been the catalysts for State actions in biotechnology in Illinois, Massachusetts, Michigan, New Jersey, New York, North Carolina, and Virginia. The oldest or largest biotechnology programs are those promoted by the Governor's office, either through a special science and technology task force or commission, or through the executive mission agencies such as commerce or economic development.

One of the earliest efforts to promote biotechnology at the State level is in North Carolina. The North Carolina Biotechnology Center was founded in 1981 under the leadership of then Governor James B. Hunt to "stimulate multi-institutional and multi-disciplinary research and education programs in science areas related to biotechnology." Originally operated from the Governor's office, this agency is now a freestanding quasi-governmental organization funded by a legislative appropriation to the North Carolina Department of Commerce, with matching funds from industry.

The State of New Jersey has also initiated an ambitious biotechnology program, stemming from recommendations of the Governor's Commission on Science and Technology. The Commission studied the makeup of the New Jersey economy, examined the potential of high-technology industries, and eventually recommended the establishment and construction of a network of advanced technology centers at the State's public and private institutions.

More recently, Wisconsin's Governor established a special State council to accelerate economic development in biotechnology. Members of the Council will include the secretaries of the State Departments of Development, Natural Resources, and Agriculture, Trade, and Consumer Protection. The Council will be chaired by the chief executive officer of Universal Foods Corporation, a large food processing and production corporation.

Mission-oriented State agencies in the Governor's executive offices have served as catalysts for biotechnology programs in other States. Most typically, biotechnology promotion has arisen from the Governor's Office of Economic Affairs, Economic Development, or Department of Commerce. This is the case in Colorado, Iowa, Kansas, Massachusetts, Michigan, Minnesota, Nebraska, Oklahoma, Pennsylvania, Utah, and West Virginia. Most notable of these efforts are programs in Massachusetts and Pennsylvania. The Departments of Commerce in these two States have led the way in devising and implementing new State initiatives to stimulate technology research and education.

In Pennsylvania, the Ben Franklin Partnership Fund, established in 1982 with a $1 million Challenge Grant Program, established four advanced research centers. These funds provided the incentive for Pennsylvania State University to construct a building to house the Penn State Biotechnology Institute, which will receive Ben Franklin Funds. In addition, in 1987, Pennsylvania's Governor released $14 million in State funds for the Pittsburgh Biomedical Research Center at the University of Pittsburgh (expected by the Governor's office to be a major biotechnology research center). The Biotechnology Center will be built on the 48-acre site of a former steel company plant beside the Monongahela River. The Pittsburgh Technology Center, of which the Biotechnology Center is a part, is expected to create more than 1,600 jobs and attract $70 million in private investment. Planners calculate that more than $1.2 million in local tax revenue will be generated by the Center. This is an explicit example of the expectation that high-technology, biotechnology in

Applied Biosystems
470A Protein Sequencer

Photo credit: Biotechnology Center, University of Wisconsin-Madison

Research scientist records the progress of a protein sample on the Gas Phase Sequencer at the University of Wisconsin Biotechnology Center.

particular, will play a central role in revitalizing a region historically reliant on manufacturing.

Role of the University in State Biotechnology Programs

Universities are often important components in State economic development initiatives, particularly in high-technology, which requires a highly skilled work force. The availability of skilled labor is the most influential factor in the regional location of advanced technology firms (12). During the 1960s, U.S. universities responded to external and internal pressures to undertake additional research and problem-solving activities that related to the needs of the Federal Government and the cities. In the 1970s, universities sought to join with State governments to address a wide array of domestic issues. In the 1980s, universities are increasingly forging new partnerships with industry to accelerate the rate of scientific and technological innovation (2).

University service to the public is not new. Agriculture has long been the model of federally assisted public service by the university, through the Land Grant System (dating back to the Morrill Act of 1862). In 1962, NASA created the Sustaining University Program (SUP) to strengthen university research programs relevant to NASA missions. SUP was phased out in 1971 after being deemed a failure. NASA administrators felt that the universities had failed to respond to NASA goals, and observers felt that NASA's goals were unrealistic, "stemming from insufficient understanding of the nature of universities" (6).

In 1967, the National Science Foundation's (NSF) Intergovernmental Program was started to promote the use of scientific and technological resources by State and local governments. In 1977, NSF implemented the Science, Engineering, and Technology (SSET) program to provide grants to governors and State legislatures for plans that would improve their use of science and technology. Implementation funds for these plans were insufficiently provided and the program was abandoned in 1981. Several of the programs the States now support grew out of strengths identified under the SSET program.

The intent of these Federal programs was to have university faculty take responsibility for the transmission, as well as the generation, of the knowledge they produce. Public universities have historically been entangled in multiple role expectations: ivory tower, service station, and frontier post (7). Philosophical differences regarding appropriate roles for educational institutions continue to influence discussions about the effects of public expectations on the quality of the research agenda and education.

In terms of biotechnology, the situation is no different. **Biotechnology owes much of its growth to academic science**. Not only has industry turned to the university as the source of cutting-edge research, but the States are also turning to their universities as the base of their biotechnology efforts. Many States recognize the value of a strong university system in attracting biotechnology companies. By creating expertise in the university system, States hope to attract and retain dedicated biotechnology companies as well as major pharmaceutical, chemical, and agricultural corporations. At the least, this form of educational investment policy infuses the universities with more resources for research and training, and at the most, attracts or creates a new technology base in the region.

Of the 33 States reporting State-supported biotechnology programs, 28 say they will rely primarily on their higher education institutions for the design and performance of biotechnology research and training. Early concerns about the influence of commercial biotechnology on universities seem not to be an issue in State-university initiatives (see also ch. 7). Public universities have traditionally cooperated with their State governments in programs to promote economic growth.

In 14 States, the university system has been the impetus for creating a biotechnology program, rather than being initiated by the State legislature or Governor's office. This is especially true in Texas, which has no Statewide biotechnology plan, and in California, where the university system has historically played a dominant role. Table 4-3 lists States where the university has been the promotional base for biotechnology rather than the Governor's office or the State legislature.

In many States, such as California, the department of higher education has led in promoting and implementing biotechnology programs, often independent of Executive action. In California, State-level promotion did not occur until 1985, well after California led in the number of biotechnology firms. The University of California (UC) System houses seven diverse biotechnology programs. San Diego State University and Stanford University also have centers. In addition, the University of California has established a multiyear effort to address the needs of biotechnology industries. This program, the Biotechnology Research and Education Program, is designed to facilitate the basic research underlying biotechnology and the training of future scientists at the nine campuses and three affiliated National Laboratories. Some would contend that the strength of the UC system has been the instrumental force in establishing a healthy biotechnology industry in California. The climate, a large venture capital pool, and expanding markets are additional inducements to industry.

In South Carolina, the push for economic development through high-technology has come largely from its universities. In 1986, the presidents of the State's three major universities announced plans for a 5-year joint research program totaling $600 million, of which a biotechnology

Table 4-3.—States Where the University Is the Promotional Base for Biotechnology

California
Florida
Georgia
Idaho
Louisiana
Maryland
New Hampshire
North Dakota
Ohio
Oregon
South Carolina
Tennessee
Texas
Wisconsin

SOURCE: Office of Technology Assessment, 1988.

center would be a small part. In Florida, Georgia, Idaho, Louisiana, Maryland, Oregon, and Wisconsin, biotechnology programs have also been developed primarily at the university level. Although biotechnology programs have not been promoted at the State level in Oregon, the Oregon Health Sciences University, the University of Oregon, and Oregon State University have spent considerable sums promoting biotechnology initiatives on their campuses.

The university-driven approach sometimes draws controversy. In 1987, the University of Georgia broke ground for a $32 million Biological Sciences Complex dedicated to research in recombinant DNA, molecular biology, and gene splicing. The Center is to be funded from the University's general instruction budget without any new or additional allocations from the university regents to cover the new positions created. As a result, other areas of the university are temporarily underfunded, drawing criticism from both faculty and students.

In Maryland, the University of Maryland has formed the Maryland Biotechnology Institute (MBI), comprised of five initiatives linked to the two campuses. As mentioned earlier, one center, the Center for Advanced Research in Biotechnology (CARB) has support from Montgomery County, MD ($9 million), and from the National Bureau of Standards (NBS) of the U.S. Department of Commerce. Although much of MBI's funds come from the State through the Department of Higher Education, the Governor's office provides no oversight. MBI plans an agenda in biotechnology R&D in the areas of agriculture, biomedicine, marine science, public policy, and protein engineering. All but the agricultural biotechnology centers were operational by 1987; it took several years to get the programs up and running. Critics of the late operational date charged that operating a biotechnology initiative under the guise of economic development may not be a manageable proposition for a university to undertake without State guidance.

Centers

Centers have become popular in the perception of the promise they hold for promoting economic development through biotechnology R&D. Usually based at universities, centers are multipurpose institutes created to foster interdisciplinary research, intercampus cooperation, and public-private collaboration. Centers can also provide technical and information assistance to university and industry scientists, and in some cases offer financial assistance to new firms. Table 4-4 lists discrete university-based biotechnology centers by State.

Centers differ in their evolution and structure. Some States with biotechnology initiatives do not have a center, but offer other incentives for R&D, such as grants and loans to both industry and academia. Altogether, 28 States have established centers or programs devoted specifically to research in areas directly related to biotechnology. In most cases, State funds were dispensed to one higher education facility for the creation of a research program. In some States—Colorado, Massachusetts, North Carolina, Pennsylvania, and Tennessee—the program is decentralized, with several State colleges and universities the beneficiaries of research and facility funds.

Not all centers that appear on paper are, as yet, operational. Many of the centers have been founded only within the past two years. The years indicated in table 4-4 represent year of founding, not year of operation. In some cases, funds have been authorized but not appropriated; in other cases, funds have been appropriated but not spent. Some centers are waiting for the construction of facilities and are operating ad hoc out of several departments within a university. In some States, the participation of several interests—State government, university administrators, and private donors—has created a complex bureaucratic network that has slowed action.

Table 4-4 also lists the substantive areas of concentration in the research programs of these centers. In most cases, several research areas in biotechnology are being pursued in a strategic manner. The university's existing departmental strengths, or the technological needs of the surrounding industrial base, provide the focus for development of specific capabilities. Newer, smaller programs, such as Connecticut's, have not yet targeted a specific area of research for funding, but will rely on newly recruited faculty to set a program agenda.

Table 4-4.—Biotechnology Centers Receiving Some State Support

Arizona
- Program for Excellence in Biotechnology (1986)
  University of Arizona, Tucson
  (biomedical)

Arkansas
- Biotechnology Institute (1985)
  Biomass Research Center
  University of Arkansas, Fayetteville
  (cell fusion, hybridoma, and monoclonal antibody technologies)

California
- Biotechnology Research and Education Program (1985)
- University of California
  Molecular Biology Institute, Los Angeles (1985)
  Biotechnology Program, Davis (1986)
  Center for Molecular Genetics, San Diego
  Center for Genome Biology, Riverside (1984)
  Plant Biotechnology Unit, Berkeley
  Gene Research and Biotechnology Program, Irvine (1983)
  Marine Biotechnology Center, Santa Barbara (1989)
- Molecular Biology Institute
  San Diego State University
- Center for Molecular and Genetic Medicine
  Stanford University

Colorado
- Colorado Institute for Research in Biotechnology (1986)
  University of Colorado,
  Colorado State University, and
  Health Sciences Center
  (reproductive physiology, fermentation, bioprocessing, agriculture, medicine, plant genetics)

Connecticut
- Biotechnology Center (1986)
  University of Connecticut, Storrs

Georgia
- Research Center for Biotechnology (1983)
  Georgia Institute of Technology
  (microbial, agriculture, biomedicine, bioreactors)
- Biological Sciences Complex (1987)
  University of Georgia
  (agriculture, medicine, energy)

Illinois
- Biotechnology Center (1986)
  University of Illinois, Urbana-Champaign
  (agriculture)
- Center for Plant Molecular Biology (1987)
  Northern Illinois University

Indiana
- Agrigenetics Research Center (1985)
  Purdue University
- Molecular and Cellular Biology Center (1985)
  Indiana University

Iowa
- Molecular Biology Program (1986)
  Iowa State University, Ames
  (agriculture, bioprocessing, food processing)

Kansas
- Center for Bioanalytical Research (1985)
  University of Kansas

Kentucky
- Biotechnology and Genetic Engineering Center (1987)
  University of Kentucky, Lexington

Louisiana
- Biotechnology Institute (1985)
  Louisiana State University

Maryland
- Maryland Biotechnology Institute (1984)
  University of Maryland
  (protein folding, crystallography, marine biotechnology, biomedicine, agriculture, policy)

Massachusetts
- Biotechnology Center of Excellence (1985)
  Massachusetts Biotechnology Research Institute
  Massachusetts State Colleges and Universities

Michigan
- Michigan Biotechnology Institute (1982)
  (fermentation, biomaterial products technology, waste treatment, industrial enzyme technology)

Minnesota
- Biotechnology Research Center (1983)
  Plant Molecular Genetics Institute
  Human Genetics Institute
  Institute for the Advanced Studies of Biological Process Technology
  University of Minnesota

Missouri
- Molecular Biology Program (1987)
  University of Missouri, Columbia
  (development and aging, disease resistance, energy, environmental applications)

New Jersey
- Center for Advanced Biotechnology and Medicine (1986)
  Rutgers University
  (biomedicine, protein science, structural biology)
- Center for Agricultural Molecular Biology (1987)
  Rutgers Cook College
- Lewis Thomas Laboratories (1985)
  Princeton University

New York
- Center for Medical Biotechnology (1983)
  SUNY Stony Brook
- Center for Biotechnology in Agriculture (1983)
  Cornell University

North Carolina
- North Carolina Biotechnology Center (1981)
  Duke University
  University of North Carolina
  North Carolina State University
  (bioelectronics, bioprocess engineering, marine, monoclonal lymphocyte technology)

Ohio
- Edison Animal Biotechnology Center (1984)
  Ohio University
  (livestock enhancement)
- Biotechnology Center (1986)
  Ohio State University
  (plant and microbial interactions, neurobiotechnology)

Oregon
- Center for Gene Research and Biotechnology (1983)
  Oregon State University, Corvallis
- Institute of Molecular Biology (1983)
  University of Oregon, Eugene

(continued on next page)

Table 4-4.—Biotechnology Centers Receiving Some State Support—Continued

Pennsylvania
- Biotechnology Institute (1987)
  University of Pittsburgh
- Biotechnology Institute (1984)
  Pennsylvania State University
  (environmental microbiology, bioprocessing, plant and animal cell culture, biomolecular structure and function)

Tennessee
- Tennessee Center for Biotechnology (1986)
  Tennessee State University System
  (plant cell tissue culture, hazardous waste management, environmental toxicology, drug delivery systems)

Texas
- Central Hybridoma Facility (NSF support 1985-1988)
  University of Texas, Austin
- Institute of Biosciences and Technology (1987)
  Texas A&M
- Institute of Biotechnology (1987)
  University of Texas Health Science Center, San Antonio

Utah
- Center of Excellence in Biotechnology (1985)
  Utah State University
  (plant and veterinary, biomedicine)

Virginia
- Center for Biotechnology (1985)
  Old Dominion University
- Institute of Biotechnology (1985)
  Medical College of Virginia of Virginia Commonwealth University
  (vaccines, biocatalysis, diagnostics)

Wisconsin
- Biotechnology Center (1984)
  University of Wisconsin, Madison
  (fermentation, biopulping, biocomputing, hybridoma, plant cell and tissue culture, sequencing and separation, enzyme improvement and production)

SOURCE: Office of Technology Assessment, 1988.

State Expenditures in Biotechnology

The States vary widely in the amount of funds they dedicate specifically to biotechnology. A multitude of problems arise if one tries to conduct an accurate comparison of State spending:

- **Few States list biotechnology initiatives as a distinct line item in their budget**. Those that do, such as New Jersey, North Carolina, and Massachusetts, provide an accurate figure for actual dollar support for biotechnology. In most States, however, the funds derive from several sources in the general funds and are directed to several recipients. Because of this, undercounting or overcounting can occur. In undercounting, for example, States that fund a Center of Excellence in Biotechnology might not count State support for biotechnology activities going on within the university system but outside the Center. For example, although the budget for the Massachusetts Biotechnology Center of Excellence only received an appropriation of $935,000 in 1987, this excludes $9 to $12 million of State appropriations for biotechnology activities at public universities and $26 million worth of biotechnology loan portfolios of State agencies. As an example of overcounting, States might report that a large portion of their health science budget is related to biotechnology without systematically verifying the claim.
- **Most States provide the operating budget for a biotechnology program, but cannot easily segregate the amount of the budget derived solely from State coffers**. Funds are categorized by type of expenditures rather than source of funds. Therefore, budgets often reflect funds derived from State appropriations, private donations, and Federal grants and contracts. With time and patience this information could be untangled. **In the OTA survey, respondents were asked to report on the amount of investment by the State only**. Calculated estimates were provided by many States in lieu of actual expenditures.
- **Respondents often had the difficulty faced so frequently by those asked to account for biotechnology activities: that of definition**. While some States define biotechnology narrowly, others consider spending in related areas to be relevant and include that in their figures. **In all cases, respondents were asked to use the OTA definition of biotechnology for accounting purposes.**
- **Some States were unable to separate funds spent specifically on biotechnology**. For

Table 4-5.—State Allocations for Biotechnology R&D, Training, and Facilities

State	FY 1986	FY 1987
Arizona	$1,170,000	$1,540,000
Arkansas	757,173	800,000
California	2,500,000	2,500,000
Colorado	500,000	500,000
Connecticut	665,000	1,100,000
Florida	5,050,000	7,050,000
Georgia	2,600,000	3,000,000
Idaho	438,800	450,000
Illinois	4,500,000	5,000,000
Indiana	4,000,000	1,029,904
Iowa	500,000	3,750,000
Kansas	162,000	172,000
Kentucky	908,500	896,600
Louisiana	670,000	NA
Maryland	2,600,000	3,900,000
Massachusetts	485,000	935,000
Michigan	6,000,000	4,000,000
Minnesota	1,032,000	1,100,000
Missouri	1,500,000	3,700,000
New Hampshire	150,000	450,000
New Jersey	10,000,000	35,690,000[a]
New York	34,300,000[a]	[a]
North Carolina	6,500,000	6,900,000
North Dakota	1,643,090	1,601,783
Ohio	2,194,787	50,000
Oklahoma	1,584,000	1,542,000
Oregon	350,000	360,000
Pennsylvania	2,848,824	18,035,494
Tennessee	NA	800,000
Utah	110,000	500,000
Vermont	NA	300,000
Virginia	1,500,000	1,750,000
Wisconsin	190,000	418,000

NA: Not available.
[a] Indicates a multi-year appropriation.

SOURCE: Office of Technology Assessment, 1988.

example, Illinois has allocated $3 million to 16 Technology Commercialization Centers that serve other high-technology interests as well as biotechnology. Therefore, its total reported budget for biotechnology can only be estimated and could be inflated or undercounted.

- **Those States responding that they have no special programs in biotechnology could be subsidizing research through a research fund or through the usual support of their universities**. For example, Texas reports no State-level program aimed at funding biotechnology, although biotechnology research is funded through general research funds available from the State. The University of Texas, Austin, supports biotechnology by housing the Central Hybridoma Facility, which was funded by the National Science Foundation at $120,000 a year until 1988 when the university had to absorb the cost. Texas A&M plans to spend $24 million to build an Institute of Biosciences and Technology to study and market developments in biotechnology. And Dallas billionaire H. Ross Perot has contributed to the construction of a research park in San Antonio that will be called the University of Texas Institute of Biotechnology.

Given these caveats, table 4-5 presents levels of direct support for biotechnology as reported by 49 States for fiscal years 1986 and 1987 (Alaska did not respond). Support includes funding of research, facilities, and training.

The range for reported spending varied from $110,000 in Utah to a $34.3 million multi-year appropriation by New York in fiscal year 1986. Several States emerge as the frontrunners in terms of dollars spent. New York and New Jersey surpass all States in spending for fiscal year 1986; North Carolina, Michigan, and Florida followed, spending over $5 million each. Pennsylvania, which spent only $2.8 million in fiscal year 1986, has accelerated its biotechnology program dramatically in fiscal year 1987, allocating over $18 million, not including matching funds of $13,212,900 in fiscal year 1986 and $32,840,503 in fiscal year 1987. New Jersey increased its allocation more than threefold between fiscal year 1986 and fiscal year 1987, from $10 million to $35.6 million: the $35.6 million allocation was for a capital building program comprised of $8.6 million in New Jersey Science and Technology Commission funds and the balance provided by the two collaborating State institutions.

New York State reported that it committed $34.3 million specifically to biotechnology in fiscal year 1986 and an additional $80 million on health research that "may or may not involve biotechnology." According to the Executive Director of the New York State Science and Technology Foundation, nearly 70 percent of those funds specific to biotechnology are spent on research; the remainder is spent on facilities and training. In fact, $32.5 million of the 1986 appropriation was for a building at Cornell University. The Center for Medical Biotechnology at the State University of New York (SUNY) at Stony Brook and the Center for Biotechnology in Agriculture at Cornell University each received $1 million for research funding. In addition to State funds, the Cornell center had three corporate sponsors that signed 6-year contracts totalling $2.5 million each. The SUNY center has 75 corporate sponsors, each involving specific research contracts. The New York Science and Technology Foundation awarded $250,000 in grants through its Research and Development Grants Program. Biotechnology training programs received $63,000 from the State in fiscal year 1986.

Maryland reported an allocation of $3.9 million in fiscal year 1987. This sum excludes a $9 million loan contribution from Montgomery County in the form of a building to house CARB, and the laboratory and personnel resources provided by a partner in CARB, the National Bureau of Standards.

It is not clear whether the high funding levels currently appropriated by many States will be sustainable. These initially large investments might represent start-up or catch-up costs for facilities and equipment. Many States are depending on industry to assume a share of support after the initial State appropriations. Biotechnology initiatives are long-term investments and likely to be viewed as justifiable areas for cutback or elimination by State legislatures during times of fiscal stress. For example, in fiscal year 1985, Louisiana allocated $1.53 million to the Louisiana State University System Biotechnology Institute. That funding level dropped to $270,000 in fiscal year 1986 because of the State's fiscal problems. Funding in the future is uncertain.

Mechanisms for Raising Funds

Most programs are funded through general State revenues appropriated through a direct legislative action, or through higher education funds. Eight States have a discrete legislative appropriation dedicated to a Center program in biotechnology or to a nonprofit development corporation. As stated earlier, it is easier to obtain biotechnology spending figures from these States because the funds are centralized.

Several States have taken unique approaches to raising the necessary capital for developing high-technology programs. In Iowa, a London-based chemical company withheld $8 million in capital investment in Iowa until the State agreed to provide $5 million a year for related biotechnology research at Iowa State University. In response, the Iowa legislature agreed to allocate $3.5 million from the State's lottery revenues.

In Missouri, fiscal year 1987 new State lottery revenues were devoted to education—including $3.7 million for biotechnology research. Facilities at the University of Missouri-Columbia were funded as part of a Statewide $600 million General Obligation Bond issue.

Perhaps the most impressive bond issue was a $90 million Jobs, Science, and Technology Bond Issue approved by the voters of New Jersey in 1984. Of the $90 million, $35 million is targeted for biotechnology. The bill establishes the Advanced Technology Center in Biotechnology and requires joint governance by Rutgers University and the University of Medicine and Dentistry of New Jersey. The New Jersey Commission on Science and Technology is now faced with raising new revenues.

In addition to floating public bonds, some States have relied on proceeds from natural resource revenues to fund research in biotechnology and other technologically based fields. In Michigan, dedicated oil and gas revenues flow to the Michigan Strategic Fund, which provides support for the Michigan Biotechnology Institute. Other support comes from the State's General Fund, which supports the universities. Montana funds the Montana Science and Technology Alliance through funds appropriated from coal severance tax proceeds.

Many States, such as Pennsylvania, Massachusetts, New York, and Ohio, require an industry match to supplement State appropriations. Programs funded through the Pennsylvania Ben Franklin Partnership are supported via a capital fund appropriation requiring a one to one match from the recipient (the actual match has been running four to one). The funds designated for the University of Pittsburgh Biotechnology Center, for example, are derived from the capital budget—

Photo credit: Michigan Biotechnology Institute

The Michigan Biotechnology Institute, a 120,000-square-foot business and research center funded by an industrial revenue bond issue, a low-interest State loan, and Institute funds.

the money in this case came from the State share of real estate transfer taxes. The matching funds are provided by a variety of organizations, most prominently private sector firms, but universities provide substantial in-kind support (11). A similar matching system exists in the Thomas Edison Program in Ohio. Matching private sector contributions can include cash, state-of-the-art equipment, and essential personnel, and in the case of small companies, use of facilities and equipment.

Special Incentives for Biotechnology Companies

Support of small business development and growth is a traditional State function. As a nation, the United States provides more direct support to small business development than does any other industrialized country (9). State departments of commerce and economic development have longstanding programs designed to assist small businesses. In some cases, support is offered through technical and management assistance: in other cases the support is financial or in the form of incentives.

Few States have special incentives or means of support specifically for biotechnology companies. Rather, biotechnology firms are eligible for the same benefits as those available to other small businesses or other high-technology firms. Most States recognize the need to do more than just attract firms from other States. Instead, they've come to understand the importance of aiding existing entrepreneurial companies. Small companies may receive direct assistance for expansion or R&D, or indirect assistance in the form of facilities, tax incentives, customized job training, or technical or management support. And, as many firms plan manufacturing facilities, States may find their business climate more or less hospitable than that offerred for R&D.

A few States already have a significant lead in attracting biotechnology firms, with 50 percent

Table 4-6.—State-by-State Distribution of Dedicated Biotechnology Companies

State	No. firms	Percent
California	111	27
Massachusetts	54	13
Maryland	38	9
New Jersey	24	6
New York	20	5
Wisconsin	16	4
Connecticut	13	3
Texas	13	3
Washington	13	3
Colorado	9	2
Pennsylvania	9	2
Florida	8	2
Minnesota	6	1
North Carolina	6	1
Ohio	5	1
Maine	5	1
Oregon	5	1
Virginia	5	1
Illinois	4	<1
Kansas	4	<1
Michigan	4	<1
Indiana	3	<1
Louisiana	3	<1
Utah	3	<1
Arizona	2	<1
Georgia	2	<1
Missouri	2	<1
Montana	2	<1
Nebraska	2	<1
Alabama	1	<1
Arkansas	1	<1
Delaware	1	<1
District of Columbia	1	<1
Hawaii	1	<1
Iowa	1	<1
New Hampshire	1	<1
New Mexico	1	<1
Rhode Island	1	<1
South Carolina	1	<1
Tennessee	1	<1
West Virginia	1	<1
Total	403	100

SOURCE: Office of Technology Assessment, 1988.

of dedicated biotechnology companies located in just five States. California remains the leader in number of firms, with 111 companies, or 27 percent of the U.S. industry. Massachusetts is second with 54 (13 percent), followed by Maryland with 38 (9 percent), New Jersey with 24 (6 percent), and New York with 20 (5 percent). Table 4-6 shows the geographical distribution of dedicated biotechnology companies by State.

State programs are challenging the traditional notion of the Federal Government as the major benefactor of the research community. For State governments, support of R&D is a relatively new function, although the motivation is historic—economic development. Many States now offer competitive grants programs in R&D for which anyone can apply.

Direct Financial Assistance

Direct financing of research is but one method of direct financial assistance for biotechnology companies. Direct financial assistance for expansion, a traditional method of small business assistance, is widely available through State economic development programs. Tax-exempt financing in the form of industrial revenue bonds can lower the cost to borrowers. Direct loans and loan guarantee programs are available to any business. Perceiving a need for unique financial assistance programs for high-technology companies, many States recently established programs targeted to high-technology firms. These programs may be quasi-public corporations that provide venture capital in the form of seed money. Arkansas, Arizona, California, Connecticut, Florida, Louisiana, Massachusetts, Michigan, New York, Ohio, Pennsylvania, and Wisconsin all have funds for new high-technology ventures.

Development Corporations.—Numerous States have established nonprofit development corporations or authorities to serve as forums for and overseers of State policies affecting high-technology development. These bodies may identify, develop, and apply advanced technologies for economic growth. In some States, such as Arkansas, the Science and Technology Authority can issue bonds, own patents, and enter production contracts and agreements. Development corporations award funds to both industry and universities.

Biotechnology often benefits from these science and technology corporations:

- In Indiana, the Corporation for Science and Technology awarded $4.5 million to Purdue University to conduct biotechnology research on new and improved crop strains, to improve biotechnology training methods for students, and to create a science base attractive to the biotechnology industry. Indiana University's Institute for Molecular and Cellular Biology received $1.2 million from the corporation to establish two research centers for monoclonal antibody production and for gene sequencing.

- Michigan has established the Michigan Strategic Fund which funds up to 75 percent of the costs incurred in developing products and processes important to creating jobs in the State. Genetic engineering is one of the four targeted areas of this program.
- The Massachusetts Technology Development Corporation, a quasi-public corporation founded in 1979, provides seed capital with other private investors and has succeeded in boosting private investment nearly 10 times the original amount (1). More specific to biotechnology, the Massachusetts Centers of Excellence Corporation, operated from the Governor's Office of Economic Affairs, funds research and development activities in five applied fields, of which biotechnology is one. The Massachusetts Industrial Finance Agency authorized a $1.5 million industrial revenue bond for continued expansion of the Biotechnology Research Park.
- The Center for Innovative Technology in Virginia is a nonprofit corporation targeting research in four broad areas perceived to be important to Virginia's economic future. Biotechnology is one of these four areas.
- The Innovation Partnership in Biotechnology Program in New Jersey provides nearly $500,000 to five academic research institutions. The funds are matched by industry funds and in-kind services.

In many States, university-industry collaboration is a condition for qualifying for research funds. Arkansas, Connecticut, Massachusetts, Pennsylvania, Tennessee, and Virginia all have programs requiring that proposals be submitted as a joint venture between a university and a firm. Often, awards are made on the basis of scientific and technical merit, followed by potential economic benefit to the State. University-industry relationships in biotechnology are discussed further in chapter 7.

Indirect Financial Assistance

States can help small businesses through a variety of in-kind mechanisms, such as site selection assistance, customized job training, legislation to assist in capital formation, technical assistance programs, property tax abatement, and income tax credits.

Incubator Facilities.—Research incubators provide low-cost office and laboratory space for entrepreneurs and struggling firms. Arkansas, Colorado, Illinois, Maryland, Massachusetts, and New York have constructed or are planning to construct incubator facilities specifically for biotechnology companies.

The Biomass Research Center at the University of Arkansas, Fayetteville, operates a biotechnology business incubator. Funds for the incubator were awarded by the Arkansas Science and Technology Authority. The Catalyst Bio Technology Industrial Incubator Project in Louisville, CO, is a public-private venture involving a consortium of corporate research facilities and staff of the University of Colorado at Boulder, Colorado State University in Fort Collins, and the Colorado School of Mines.

The College of Agriculture at the University of Illinois plans to build a business incubator at its research farm where scientists from industry can use university research to develop and market new farm products. Businesses will be selected for participation on the basis of their potential for developing a marketable product (within 2 to 3 years) that could be manufactured in the State and be used to help Illinois agriculture. An 11-member committee of farmers, agribusiness representatives, and university faculty will review proposals to select companies. The Illinois Department of Commerce and Community Affairs has awarded a $200,000 grant to the incubator. The university will contribute an additional $400,000.

Tax Incentives.—Taxes are important to small, expanding high-technology companies because cash flow is critical. State and local taxes take cash from a company when they need it most, at the outset of business when little or no revenues are being generated. Recognizing this, most States offer some type of tax incentive for business expansion. Efforts to provide incentives for high-technology companies have increased recently.

In 1981, California eliminated taxes on capital gains for investments in eligible "small business stock" held for 3 or more years, a novel approach that encouraged additional venture capital investments in startups and other small businesses. The State of Indiana allows a tax credit of 30 percent on individual investments in a venture capital pool administered by the Indiana Corporation for Innovation Development (15). Minnesota encourages technology development and spin-offs by offering a tax credit of 30 percent of the value of the technology transfer that occurs when a small business is spun off from a parent firm.

Arkansas offers State R&D tax credits, and Iowa offers property tax abatement and State income tax credits for high-technology firms.

Information and Technical Assistance.—According to a 1983 survey by the Council of State Governments, 48 States offer general business information or related technical assistance (10). This assistance may include site location, permits, labor force availability, or accessibility to databases.

Increasingly, States are designing technical assistance programs to match innovators with investors. A venture capital network created in New Hampshire consists of databases of entrepreneurs and their ideas and individuals wanting to make investments. The Wisconsin Innovation Center helps inventors evaluate the commercial feasibility of their ideas and inventions. Only one State has designed a program specifically for biotechnology companies: the North Carolina Biotechnology Center has compiled a compendium of North Carolina scientists conducting biotechnology research and a list of North Carolina biotechnology companies and their activities.

Arizona, Kansas, and New York have programs to assist companies applying for Federal Small Business Innovation Research (SBIR) dollars. In Arizona, the Arizona Innovation Network and Arizona State University have formed a consortium that is expected to help small technology companies reap the benefits of the SBIR program. New York State sponsors the SBIR Promotion Program. Chapter 3 describes the extent to which SBIR funds have been used to assist biotechnology firms.

THE NATIONAL SCIENCE FOUNDATION EXPERIMENTAL PROGRAM TO STIMULATE COMPETITIVE RESEARCH

For a few States, Federal assistance has provided a new opportunity for developing biotechnology. In 1978, the National Science Board of the National Science Foundation (NSF) responded to concern over the geographical distribution of awards by initiating the Experimental Program to Stimulate Competitive Research (EPSCoR). This program aims to improve the quality of the science and engineering research environment in States that are least successful in competing for Federal R&D awards.

The EPSCoR program is conducted in two phases: a planning Phase A and an implementation Phase B. In Phase A, States are given nine months and a $125,000 planning grant to assess their science and technology base and to develop a 5-year research improvement plan. Phase B awardees receive additional funds to enhance their scientific and technical base. Awards are based on scientific merit and local commitment to improving science and engineering. In the first round—1985—NSF awarded 5-year Phase B grants ranging from $2.4 million to $2.9 million each to Arkansas, Maine, Montana, South Carolina, and West Virginia.

In 1986, the National Science Board awarded Phase B grants totaling $23.5 million to another set of jurisdictions—Alabama, Kentucky, Nevada, North Dakota, Oklahoma, Puerto Rico, Vermont, and Wyoming. In turn, the States and Puerto Rico pledged a total of $67.9 million to help implement their EPSCoR programs.

At least five States plan to use the EPSCoR funds to build on their expertise in biotechnology:

- Vermont will use the funds to create faculty positions in recombinant DNA and molecular biology at the University of Vermont (4). The State plans to match the EPSCoR funds with $300,000 to fund research projects in areas relevant to biotechnology.
- In North Dakota, the EPSCoR funds are contributing to a $250,000 program in Cellular

and Molecular Biology at North Dakota State University (3).

- The Montana Science and Technology Alliance has targeted biotechnology as one of eight technology areas under consideration for funding.
- The University of Kentucky has designated biotechnology as one of the Centers of Excellence in its 5-year plan and the EPSCoR plan. EPSCoR funds are dedicated to a Membrane Sciences Research Program in a newly formed Biotechnology and Genetic Engineering Working Group.
- In Oklahoma, $303,000 and $323,000 of the EPSCoR funds were spent on biotechnology in fiscal year 1986 and fiscal year 1987 respectively.

While it is too early to assess the extent to which EPSCoR funds will help certain States gain a foothold in biotechnology, it is clear that biotechnology is a field some States had in mind when developing their strategic plan for Phase A of the EPSCoR program.

SUMMARY AND CONCLUSIONS

Thirty-three States reported to OTA that they are actively engaged in some form of promotion of biotechnology research and development, as a means of academic excellence in their colleges and universities, and as a path to economic development. Six additional States are studying the feasibility of a special initiative within their borders. Clearly there is room for many players, and the Nation will benefit from the role that States can play in funding basic and generic applied research in biotechnology. Whether these programs will yield returns within an acceptable policy cycle will depend on the patience and commitment of State policymakers and their public. It is inevitable that States will compete with each other in the race for excellence in biotechnology. Many factors contribute to a firm's decision to locate within a State. New State programs to attract firms and faculty can only address some of those factors. At best, this interstate competition will create the net effect of a positive business environment in most States and localities. **Furthermore, as biotechnology firms establish separate manufacturing facilities, a new set of criteria could influence site selection than was used in siting R&D facilities.**

The early influx of Federal dollars into defense and aerospace research in regions such as Research Triangle Park, Route 128, and Silicon Valley played a major role in establishing a successful high-technology economy for North Carolina, Massachusetts, and California, respectively. These three well known regions of high-technology development owe their early growth and success, in large measure, to Federal spending for R&D. In the future, no one region or State may be able to dominate Federal funds in the manner these States have in the past. Federal research dollars are now more widely disseminated. However, those States with universities that receive a large share of Federal biological and biomedical research funding will retain an advantage over those that are still struggling to establish a strong research capability.

It is too early to tell who the winners will be. The only available measures of strategic position to date are the age of the program, the size of its budget, and the number of biotechnology companies already established within a State's borders. The oldest biotechnology program—in North Carolina—is only in its seventh year. And although it is the oldest program, it is not funded at the highest level.

The problem of inadequate and differing performance measures will remain. Some States will consider their programs a success if they achieve research excellence in their universities. Others will measure success by the growth of the biotechnology industry within their borders. Ultimately, the success of a State initiative must be judged from the State or local perspective. Officials with a long-term view and the patience to wait will realize that the benefits of investment in biotechnology may be far in the future. Biotechnology is not a big employer. Small biotechnology companies do not require large physical plants. Biotechnology is a research-intensive field with a longer lead time to the marketplace than other fields, particularly in view of the need for regulatory review of many of its products. In this sense, biotechnology differs greatly from other high-technology areas, such as microelectronics, where the time between invention and sales can be relatively short. The real payoff to investment in biotechnology probably will be technologically based. That is, strategic investment in biotechnology may yield applications (e.g., new crops, pesticides, or health care) that might genuinely effect change in the State's economic or industrial base. **Thus, it will be more the application of the technology that transforms the economy, not a new work force or a taxable physical plant.**

The mode and philosophy of economic development varies greatly from State to State. Those States with the earliest and most ambitious programs, such as North Carolina, Massachusetts, and New Jersey, have all had strong leadership from the Governor's office. In each of these States, the Governor assumed the role of chief economic development officer, making a profound impression by his personal involvement in the economic development process. State biotechnology programs with strong support from their governor could fare better than those trying to muster resources haphazardly without an explicit executive endorsement.

Initiatives need to be keyed to each State's existing economic and academic base. The development of high-technology industry results from close cooperation with academic centers of excellence, the availability of highly skilled labor and sufficient risk capital, aggressive venture capitalists, and proximity to Federal research dollars and facilities.

Long-term research programs run counter to the tradition of quick turn-around on State investments. **But States could lead all levels of government in the design of applied research programs and could succeed in areas where the Federal Government will not**. For those States able to sustain their investment for a prolonged period of time, biotechnology could serve them and the Nation well. States facing fiscal stress, educational insufficiencies, and severe unemployment could find such long-term investment a difficult prospect.

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Chapter 5

U.S. Commercial Biotechnology

"Biotech company officials are spouting projections that have no reality. They whip up the public's imagination every time they rinse out a petri dish."

George Sasic
Thomson McKinnon Securities
Changing Times 6-21-87

"Keep on dancing—but choose partners carefully."

Peter Drake
Kidder Peabody

"I believe God created stockbrokers so they can tell biotech managers how to promote their companies effectively."

Richard A. Bock
Bear, Stearns & Co.
Bio/Technology, October 1986

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Chapter 5

U.S. Commercial Biotechnology

INTRODUCTION

Huge public and private investments have been made in biotechnology since the venture capital community first recognized the potential profitability of Genentech, the first dedicated commercial biotechnology company to go public. Since the formation of Genentech in 1976, several hundred companies have formed, and major U.S. corporations have invested considerable sums in research and development (R&D) in biotechnology.

Biotechnology has captured the interest of the public and Wall Street, yet both have been occasionally disillusioned by the risks and revised time frames for introducing commercial products. Financial markets have reflected the turmoil of regulatory uncertainties, imbalance in the public markets of supply and demand of biotechnology stocks, the high value of the dollar, disinflations, and economic adjustments (25). There is no doubt that biotechnology has arrived as an important tool for industrial innovation; the question remains how the private sector will divide the processes, products, and proceeds of its development and sales. The comparatively smaller biotechnology companies continue to provide many of the innovative new ideas although larger, established corporations are increasingly improving their in-house R&D potential. Mutually beneficial arrangements have been worked out between the two groups.

For the purpose of this report, OTA designates firms as either dedicated biotechnology companies (DBCs) or large, diversified companies employing biotechniques. **DBCs** (referred to as new biotechnology firms or NBFs by OTA in 1984) are entrepreneurial ventures started specifically to commercialize innovations in biotechnology (35). Because many of these firms are no longer new, and some are quite established, the term "dedicated biotechnology companies" is more likely to stand the test of time than the early term NBF. Largely diversified companies commercializing biotechnology tend to be older and pursue multiple product lines, many unrelated to biotechnology.

This chapter reports on two surveys conducted by OTA in 1987.[1] The original 296 U.S. dedicated biotechnology companies contacted were chosen for their direct and focused involvement in recombinant DNA technology, monoclonal antibodies, and cell culture. The sample was developed from several directories of biotechnology firms compiled annually, including: Sittig and Noyes Directory of Biotechnology Companies; Walton and Hammer Genetic Engineering and Biotechnology Yearbook; *Genetic Engineering News* Directory of Biotechnology Companies; *Bioengineering News* Bio1000; and SCRIP Directory of Biotechnology Efforts in Pharmaceuticals. Of the 296 companies contacted, 136, or 46 percent, responded to the survey questionnaire. Survey data were supplemented, where possible, with press reports, annual reports, and other public information. Companies responded to questions regarding level of R&D investment, number and nature of employees, methods of financing, patent expectations, and product lines. A list of dedicated biotechnology companies, identified by OTA as of January 1988, appears in appendix A. More companies were identified than surveyed.

In 1987, OTA surveyed 53 large corporations known to be investing in biotechnology R&D either in-house or through strategic alliances with DBCs. Companies were selected from previous OTA databases, trade associations, publications, and personal communications with biotechnology industrialists. Companies were asked to report on the level of investment in biotechnology R&D, commitment in terms of full-time employees, sources of innovation, existing and expected biotechnology product lines, patent applications, and use of trade secrets. A list of corporations identified by OTA as being involved in biotechnology also appears in appendix A.

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[1] The North Carolina Biotechnology Center conducted a survey, under contract with OTA, of dedicated biotechnology companies. The Center for Survey Research in Boston, MA, under contract with OTA, surveyed large diversified companies.

The data collected from these two surveys are limited. Ideally, the best way to measure investment would be to first identify, then survey each and every firm involved in biotechnology. Identification of firms is itself problematic. New firms form, and others go out of business or are acquired. Some firms call themselves biotechnology companies when, in fact, they do not meet the OTA definition. Other more traditional firms may be conducting important research in biotechnological areas, but do not consider themselves biotechnology firms, and do not identify themselves as such. Large corporations may be multinational, with several subsidiaries, making identification of programs and budgets complex.

Even after compiling a reliable list, there is the additional problem of gathering information from the companies identified. Firms that are privately held—as defined by the Securities and Exchange Commission—often do not wish to divulge financial information, inevitably resulting in undercounting. Some forms of investment by public firms, such as research contracts or licensing agreements, need not be divulged, compounding the problem. **Thus, any accounting of total private investment in biotechnology is likely to be an underestimate.**

In addition to discussing the results of these surveys, this chapter reports on an analysis of 552 collaborative ventures between U.S. firms and between U.S. and foreign firms that occurred between 1981 and 1986. **Collaborative business ventures between U.S. firms have risen steadily over the past 5 years, while those between U.S. firms and foreign firms have remained stable.**

PROFILE OF COMMERCIAL BIOTECHNOLOGY

While biotechnology has taken on a "trade" status with its own firms, newsletters, investment funds, and regulations, it is not a single industry but a set of enabling technologies applicable to a wide range of industries. Thus, the term "the biotechnology industry" is somewhat of a misnomer. The industry is by no means homogeneous, but comprised of many sectors, each facing its own unique advantages and hurdles.

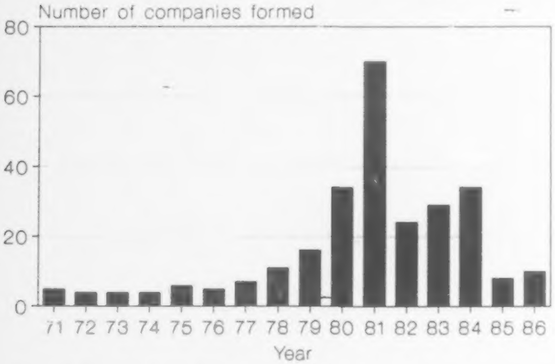
Within the broad categories of DBCs and large, diversified corporations are many traditional industrial sectors: pharmaceuticals, plant and animal agriculture, chemicals, energy, waste management, and ancillary industries that will supply users with equipment, reagents, and information systems. Each sector faces different financial markets, public markets, regulatory requirements, intellectual property issues, personnel needs, and gaps in knowledge needed for commercialization. As the tools of biotechnology are integrated into various sectors, the barriers to commercialization more closely resemble those facing the entire sector or those historically faced by entrepreneurs or multinational corporations—evidence of the growing maturity of biotechnology as an integral part of modern industry. An in-depth discussion of investment and commercialization issues in human therapeutics, plant agriculture, and hazardous waste management appears in chapters 9, 10, and 11.

Formation and Growth of U.S. Commercial Biotechnology

The boom for founding dedicated biotechnology companies occurred between 1980 and 1984. During these years, approximately 60 percent of existing companies were founded. Figure 5-1 illustrates the number of biotechnology companies founded per year between 1971 and 1986. The peak year was 1981, with nearly 70 new firms formed.

OTA verified that, as of January 1988, 403 dedicated biotechnology companies are in business and are actually working in the area of biotechnology. In addition to the presence of DBCs, over the past 5 years, major U.S. corporations have increasingly invested large sums in in-house biotechnology research and in joint ventures, acquisitions, licensing, and marketing agreements with smaller

Figure 5-1.-Founding of U.S. Dedicated Biotechnology Companies, 1971-86



SOURCE: Office of Technology Assessment, 1988.

biotechnology companies, and in research contracts with universities. OTA identified 70 major corporations with significant investments in biotechnology (see app. A) of which 53 participated in a 1987 survey. It is important to note that some are subsidiaries of others, and others conduct their biotechnology research solely overseas.

The "biotechnology industry," if measured by the entry of new, small companies in the field, has most likely stabilized. Some analysts would contend that, due to consolidation within the industry and the predominance of a few firms, the number of **viable** DBCs is actually shrinking. The industry as measured by the amount of money invested by large diversified corporations and DBCs, however, is growing.

Areas of Commercial Application

A human health care focus—therapeutics and diagnostics—continues to dominate both biotechnology R&D and the market in terms of volume. Human health care comprises the primary biotechnology work of 39 percent of DBCs and 37 percent of large, diversified companies. Human therapeutics clearly dominate the focus of most firms, large and small. Among the DBCs, therapeutics represent the primary interests of 21 percent of the respondents; the percent is slightly larger among corporate investors at 26 percent. Human diagnostics rank second as an area of R&D focus by DBCs (18 percent) but fourth by larger companies (11 percent). Therapeutics and diagnostics are considered separately because they tend to be pursued by different industries and are regulated differently by FDA (ch. 9). The strong focus on human health care products by DBCs is not unexpected. Historically, capital availability has been greater for pharmaceuticals than for food or agriculture because of greater market reward (3).

Animal health and agriculture are the focus of 14 percent of DBCs and nearly 21 percent of large, diversified companies. Chemicals (commodity and specialty such as polymers, enzymes, and additives) are the focus of 7 percent of DBCs, but 21 percent of the corporate sample. It is not surprising that pharmaceuticals and chemicals rate first and second as the areas of application pursued by the latter, since the pharmaceutical and chemical sectors have been the most active in terms of R&D investment in biotechnology. Table 5-1

Table 5-1.—Areas of Primary R&D Focus by Biotechnology Companies

Research area	Dedicated biotechnology companies Number (percent)	Large, diversified companies Number (percent)
Human therapeutics	63 (21)	14 (26)
Diagnostics	52 (18)	6 (11)
Chemicals	20 (7)	11 (21)
Plant agriculture	24 (8)	7 (13)
Animal agriculture	19 (6)	4 (8)
Reagents	34 (12)	2 (4)
Waste disposal/treatment	3 (1)	1 (2)
Equipment	12 (4)	1 (2)
Cell culture	5 (2)	1 (2)
Diversified	13 (4)	6 (11)
Other	51 (18)	0 (0)
Total	296 (100)	53 (100)

SOURCE: Office of Technology Assessment, 1988.

compares the fields of commercial application pursued by both groups.

The production of biotechnology reagents, such as restriction enzymes and recombinant DNA vectors, also ranks high among DBCs (12 percent). It is possible that the number of biotechnology suppliers will grow as routinization and standardization of many biotechnology processes occurs. Several small firms may find their niche as the supplier of specialized reagents. The same is true for equipment. Equally likely is the possibility that companies will turn in-house for these services, requiring less dependency on outside interests.

Most DBCs that responded to the OTA survey reported that 100 percent of their efforts are biotechnology-related. On the average they report that recombinant DNA technologies assist them in approximately 44 percent of their work, use of monoclonal antibodies underlies 36 percent of their work, and cell culture contributes to 31 percent of their work.

Anticipated Product Lines of Corporations Investing in Biotechnology

Table 5-1 lists the areas of application invested in by U.S. corporations investing in biotechnology. Eighty-nine percent expect that they will develop product lines in those areas within the next 5 years. Interestingly, nearly half of the corporate representatives stated that the anticipated product lines were different from current product lines. Twenty-eight percent indicated that the biotechnologically derived product lines were not at all like current products, indicating a trend in using biotechnology as a means of diversification. Forty percent felt that anticipated products developed from biotechnology were similar to existing products.

R&D Investment in Biotechnology

Biotechnology companies, more than others, are driven by R&D, relying on eventual conversion of the R&D into revenues. Funding and building R&D will remain a key component of the business strategy of DBCs until they have products requiring heavy financial commitments to regulatory review, manufacturing, and marketing. Established corporations have either created new biotechnology R&D initiatives in-house, redirected existing R&D efforts, or invested in biotechnology R&D conducted by other firms or university-based scientists.

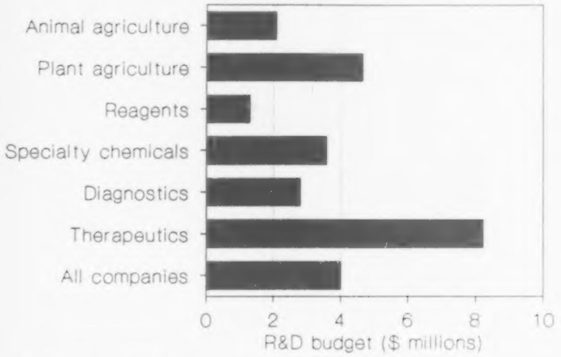
Based on responses to a 1987 survey, OTA estimates that 403 DBCs invested about $1.2 billion in biotechnology R&D in 1987, and major corporations invested more than half that amount or $0.8 billion. Because there is a good possibility that some double counting may occur due to collaborative ventures between the two groups, the combined industrial investment in biotechnology R&D is most likely in the range of $1.5 to $2.0 billion in 1987. This estimate approximates that generated by the National Science Foundation where biotechnology R&D performance by industry was estimated to be $1.4 billion in 1987 (29). Industrial investment in biotechnology R&D, therefore, is roughly two-thirds that of Federal spending.

R&D Budgets of Dedicated Biotechnology Companies

The R&D budgets for dedicated biotechnology companies surveyed by OTA had a mean of $4 million per firm, or more than 40 percent of the expected revenues. The range of responses from 108 companies was $10,000 to $45 million. The median response was $1.5 million. Genentech, for example, spent $80 million on R&D in 1986 (18). Skewing of the OTA data could be caused by the therapeutics firms, which tend to have, on average, R&D budgets of close to $9 million, higher than firms in other sectors. Differences in the size of R&D budgets are illustrated in figure 5-2.

R&D budgets are more than four times larger in public companies than in private companies. As would be expected, R&D budgets in dollar terms increase with company size, but consume the largest portion of expenditures for medium-size firms. This is most likely due to the high administrative start-up costs of small firms, the diversion of funds to other activities in large companies, and economics of scale for R&D activities. In any event, there are numerous complexities involved in measuring R&D budgets at the firm level, and it is difficult to conclude whether R&D activity, as opposed to budgets, really varies uniformly with firm size (23).

Figure 5-2.-Mean R&D Budgets for U.S. Dedicated Biotechnology Companies



SOURCE: Office of Technology Assessment, 1988.

R&D Investment by Major U.S. Corporations

Based on the responses of the 53 major corporations responding to the OTA survey, OTA extrapolates that corporate investment in biotechnology R&D approximated $0.8 billion in 1987. These companies dedicate 20 percent of their total R&D expenditures to work specific to biotechnology. Responses ranged from annual R&D expenditures of $10,000 to $150 million. The mean annual biotechnology R&D budget for these companies was $11 million in 1987.

Ninety-six percent of the respondents indicated that at least some of this R&D was conducted in-house, but 83 percent indicated that some of the research is conducted by outside firms or universities. Only four percent of the companies responded that none of their biotechnology R&D is conducted in-house. Thus, major corporations are building their in-house R&D capabilities while simultaneously complementing their research with outside sources of innovation. Collaboration between DBCs and major corporations is discussed later in this chapter.

Sources of Revenues

Gathering reliable information about actual sources of revenue in biotechnology companies is a difficult task, given the small number of products being marketed and the multiple sources of revenue available to firms. Numbers concerning products and sales can be deceiving. Plant agriculture seemingly leads in expected revenues because firms in this area are most probably also seed companies that rely on sales of seeds to fund their R&D. Diagnostics receive only about 10 percent of the overall R&D investment but account for about 55 percent of product sales (25). Revenues for diagnostics also currently lead therapeutics in sales due to the longer testing and approval process for therapeutics.

Besides being difficult to determine whether revenues have increased due to bigger research agreements or sales, it is often not entirely clear to what extent biotechnology products account for those sales being reported. Many companies are selling services or related products but have not yet sold a product directly derived from their biotechnology R&D. To date, no biotechnology company has been able to report a profit solely from the sale of biotechnology products (6).

Calgene is a case in point. In July 1986, Calgene forged agreements with Procter & Gamble and Philip Morris Co. and expanded its contracts with Campbell Soup and Rhone-Poulenc Agrochimie. It also acquired Agro Ingredients, a marketer of specialty plant oils and ingredients to industrial users and food processors. Calgene also signed an agreement with Ciba-Geigy. As a result of these new contracts, Calgene's product development revenues jumped 217 percent. Sales, which were zero the year before, totaled $882,000 as a result of the Agro Ingredients acquisition. Overall, Calgene's total revenues rose 465 percent to $2.1 million while their net loss narrowed to $329,000 from a previous year deficit (38).

Sales projections for the total industry are remarkably different, even one year into the future. One analyst predicts total industry product revenues to be about $75 million in 1987 (31). Another projects industry sales to approach $1 billion in 1987 (25). Presumably, the difference in projections can be attributed to what is being counted. For example, firms might include in their revenue totals the sale of non-biotechnology items or the sale of instrumentation, equipment, and supplies essential to biotechnology R&D.

Photo credit: Amgen

Industrial biotechnology manufacturing facility.

In calculating the worth of commercial biotechnology, most financial analysts limit their estimates primarily to biotechnology-based human health care products. No good data are yet available on sales in other sectors. The current list of human therapeutics derived from biotechnology approved for sale is still very short: human insulin, human growth hormone, alpha-2 interferon, a monoclonal antibody for reversing kidney transplant rejection, a hepatitis B subunit vaccine, and tPA. Most biotechnology products so far have been monoclonal antibody diagnostic test kits and gene probes; there are almost 200 monoclonal-based diagnostic kits. Kit sales were $150 million in 1985 (1).

Again, aggregate revenue figures can be skewed by the performance of a few firms. In the first quarter of 1987, revenues increased sharply and losses narrowed at the leading four or five DBCs. Rises were related to either increased product sales or more extensive collaborative arrangements with other companies. In 1985, Genentech posted revenues of $90 million and Cetus posted at $57 million, but sales of products accounted for only $5.1 and $1 million, respectively. Most other companies were far behind in reported revenues (less than $10 million) (1).

Even one company can skew the market averages. For example, of 18 companies analyzed in one study, total industry losses in the first quarter of 1987 were $15.3 million, but $5.4 million of those losses belonged to Monoclonal Antibodies (33). Firms record net losses as they increase their operating costs associated with proprietary research and product development.

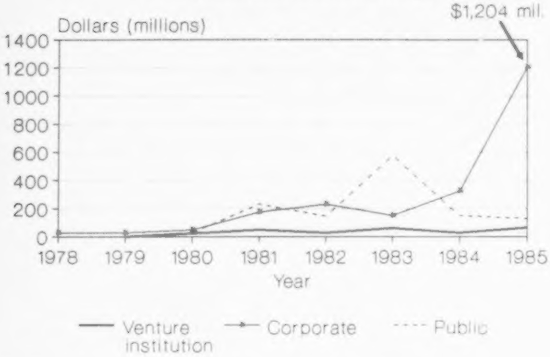
FINANCING OF DEDICATED BIOTECHNOLOGY COMPANIES

Investors have staked more than $3 billion on biotechnology between 1976 and 1986 (11). It is significant, however, that 80 percent of the dollars have been raised by 10 companies (2). Financing of biotechnology, in terms of DBCs, is quite concentrated.

Dedicated biotechnology companies have relied heavily on two funding mechanisms to finance their research and development: equity investments and joint ventures. Equity investments in DBCs may be by individuals, small financial institutions, or corporations trying to gain a foothold in the technology. The corporate source of investment is the fastest growing, rising steadily since 1983 (see figure 5-3).

The OTA survey of major corporations found that 83 percent invest in R&D conducted outside the company, either by DBCs, universities, or both. Corporations can invest in DBCs through equity or collaborative ventures. Equity investments in DBCs by large, established firms tend to be more passive, allowing the larger companies the opportunity to keep abreast of new developments. Collaborative ventures, on the other hand, usually

Figure 5-3.-Sources of Investment in Commercial Biotechnology



SOURCE: Adapted from James R. Murray & Co., Chicago, IL, 1986.

involve R&D contracts or product licensing agreements, with the larger firm often handling the final development, approval, manufacturing, and marketing of the product. The DBC receives royalties from the sale of the product and usually retains patent rights.

The sources of funding for DBCs tend to depend on company maturity and size. An increasing number of firms are turning to public offerings and corporate equity investment as their source of funding as they mature, but venture capital and private equity placement are the mainstay of start-ups. Over time, the average company shows a decreased dependence on private investment, a doubling of U.S. equity holders, and a 10-fold increase in public stock offerings.

In addition, global markets have emerged, facilitating multi-source funding for the more secure firms. The bigger companies, such as Genentech and Cetus, are able to go overseas and access the Eurobond markets. In addition, the Japanese markets have opened.

Methods of financing differ from field to field. OTA found that DBCs focusing on therapeutics are more likely to be publicly held than any other type of firm (57 percent). Plant agriculture firms are less often publicly held (20.8 percent), and specialty chemical firms are least likely to have gone public (17.6 percent). In 1987, six agricultural biotechnology firms issued an initial public offering, indicating a shift toward public capital in the future as they require additional financing to bring their products to the market.

Levels of Financing

Ninety-four DBCs responded in full to OTA requests for financial information. To date, levels of financing are five times higher in public companies than in private companies. As would be expected, financing is much higher in large companies (average 267 employees), exceeding that in small companies (average 11 employees) by nearly 20-fold.

Of those companies reporting on levels of financing, 73 percent appeared at $1 million to $50 million. Responses ranged from $10,000 to $320 million. The median response was $8 million. Values are depicted in table 5-2. Companies involved in human therapeutics report more than twice the average level of financing of all companies. Companies developing biotechnology reagents reported the least amount of financing (about one-third the average).

Sources of Investment

According to one analyst, total private investment in U.S.-based biotechnology through the end of 1985 was over $4 billion (27). These figures break down to 65 percent equity purchase ($2.581 billion), 15 percent contract research and joint venture ($578 million), 14 percent research and development limited partnerships (RDLPs) ($558 million), 6 percent grants to universities ($260 million), and 1 percent product license agreements ($4 million).

Table 5-2.—Levels of Financing of Dedicated Biotechnology Companies

Level of financing ($ millions)	Percent of companies
0 to 0.1	5.3
0.1 to 0.5	6.4
0.5 to 1	7.4
1 to 5	25.5
5 to 10	13.8
10 to 50	34.0
50 to 100	5.3
100 plus	2.1

The range is $10,000 to $320,000,000.
The median value is $8,000,000.

SOURCE: Office of Technology Assessment, 1988.

The dominant investment area is health care applications: cancer therapeutics at 43 percent ($1.7 billion), other therapeutics at 19 percent ($773 million), and diagnostics at 13 percent ($519 million), totaling 75 percent of all investment. Agricultural applications, plant and animal, have received only 16 percent of the total investment, with crop or plant improvement receiving 12 percent, or $479 million, and agrichemicals receiving 4 percent, or $154 million (27).

Analysts are more likely to agree on levels of investment than they are sales. One estimates that $3.01 billion has been raised by dedicated biotechnology companies from 1980 to mid 1987. Included in this estimate is capital raised through major R&D partnerships and corporate equity investments, plus convertible debt (2). The breakdown per year is shown in table 5-3.

Venture Capital

Practically all DBCs in existence have been the recipients of some level of venture capital, either from institutional or corporate venture capitalists. Approximately $775 million of venture capital was invested in biotechnology between 1976 and 1986, but half of that investment occurred in 1981 and 1982. Since 1982, an average of ten new companies per year have been financed by venture capital (9). Venture funding is not as sensational as it was 5 years ago, but venture funds remained available until the stock market crash of October 1987 (2,10). Until October 1987, OTA found no evidence that venture capital funds for biotechnology had diminished. There is some evidence, however, that venture capitalists are more sophisticated, and therefore more conservative, in their investment choices (36).

OTA found that the percentage of DBCs relying primarily on venture capital for financing (over half of their source of funds) dropped from 25 percent in their first year of operation to 15 percent now. As companies grow, they maintain their emphasis on venture capital, but increase their use of private equity holdings, debentures, and bank borrowings (39). Cumulatively, venture and other fund managers have provided 12 percent or $500 million of total financing. Venture funds, by the nature of their providers, tend to be short term, and they have served early-stage financing needs of many companies. As the companies continue to mature, venture capitalists may be less willing to finance forward integration.

Table 5-3.—Funds Raised by Dedicated Biotechnology Companies, 1980-87

Year	Capital raised (millions)
1980	$ 43
1981	140
1982	210
1983	542
1984	165
1985	249
1986	960
1987 (through July)	704
Total	$3,013

SOURCE: M. Kathy Behrens, personal communication, 1987.

Research and Development Limited Partnerships (RDLPs)

An important funding mechanism for the biotechnology industries has been research and development limited partnerships (RDLPs). Almost 25 percent of the dollars collectively invested in biotechnology have come from RDLPs (22). RDLPs have been described by a Commerce Department official as being a management concept and an off-balance-sheet funding source (24). They allow individuals or companies to invest in a firm's R&D and write off the investment as an expense. Investors become limited partners and are entitled to royalty payments from future sales. The royalties are then taxed as capital gains. RDLPs provide start-up companies with a source of funding and transfer much of the risk of research and development of a new product to the limited partners who have acquired shares in the ventures. They are often seen as an alternative financing mechanism to venture capital companies, and provide a vital source of capital for start-up companies.

There are obvious advantages to both the sponsoring company and its limited partners. RDLPs allow a company to avoid early negative cash flow and permit the sponsor to use its capital for other purposes. This is true as long as it can generate enough cash to make royalty payments to the limited partners. Before the Tax Reform Act of

1986 (TRA) (Public Law 99-514), RDLPs were costly for the Federal Government. As an RDLP project became more financially successful, it represented forgone taxes to the government, because some of the royalty payments could be treated as long-term capital gains that were taxed at a lower rate than ordinary income. If the company produced a patentable product, all of the royalty payments to the limited partners could be treated as capital gains. In addition, RDLP limited partners could use the losses incurred to offset their personal income, allowing RDLP investors to reduce their total income and ultimately their bottom-line tax (22). Now losses can't be used to offset income from dividends and interest, rather they can only be used to offset passive gains from other partnership investments. With the passage of TRA, capital gains rates were phased out, which may have reduced the desirability of RDLPs because gains will now be taxed as ordinary income.

Attendees at a 1987 Industrial Biotechnology Association conference agreed that despite TRA—which does not allow deductions to be used to offset salary income—RDLPs remain as an important option in the funding of biotechnology R&D (14). Financial analysts agree that investors will need near-term cash flow to help offset the loss of several tax advantages. In addition, biotechnology companies will have to make important decisions when determining the size and the content of the RDLP.

Industry representatives told OTA that although the potential size in dollar amounts of RDLPs are quite large, they are not widely available. Larger companies closer to production and marketing of products tend to use them more than smaller companies. Recently, companies such as Cetus, Genentech, and California Biotechnology have begun to buy back the partnerships, taking a one-time charge against earnings (and a subsequent loss) to finance the buyouts (5). Repurchasing allows the DBC to purchase product rights licensed to the limited partners.

One of the more innovative approaches was recently offered by Cetus. Cetus wanted to form a European subsidiary for conducting clinical trials with Cetus' investigational drugs and use the trials with results of these studies for product registration. Funding for this subsidiary, EuroCetus, would be supplemented by a $100 million RDLP. The RDLP was available to the public in $10,000 units with a minimum cutoff of $50 million. The offering was terminated after $62 million was raised due to deteriorating market conditions. Some analysts think this failure reflects a greater skepticism of investors about the ability of DBCs to develop manufacturing and marketing capabilities competitive with those of experienced and powerful incumbents in downstream sectors (34).

It is not yet clear how well RDLPs will continue to serve the R&D financing needs of the industry. A study by Arthur Young found that RDLPs are significant sources of funds for DBCs working in diagnostics and agricultural biotechnology (39). Others have argued that the market for RDLPs has all but dried up (15). OTA found that only three DBCs relied on RDLPs for more than half their funding. It is likely that RDLPs will continue to be a substantial financial tool for a select few firms.

Public Stock Offerings

Increasingly, DBCs have gone public to raise additional funds. OTA identified 82 publicly held DBCs. Of the 60 firms typically followed by Wall Street, only 27 have been able to raise $4 million or more at one time between 1981 and 1986 (7).

Currently, equity financing in the public markets accounts for 36 percent of total financing. Genentech made a historic public offering in 1980, when its stock underwent the most rapid price increase in Wall Street's history, rising from $35 to $89 per share in the first 20 minutes of trading. Later that year, Cetus raised $110 million in an initial public offering. The bull market in biotechnology had begun and would peak in 1983 (25). More than $500 million was raised for biotechnology ventures between 1979 and 1983 through public venture capital. This was followed by a period of disillusionment as investors saw the reality of the lag time between investment and payoff. In 1986, the public financing market again opened its arms to biotechnology; companies raised $800 million in 1986 through public equity markets. In the first half of 1987, $357 million had been raised through public financing, with a

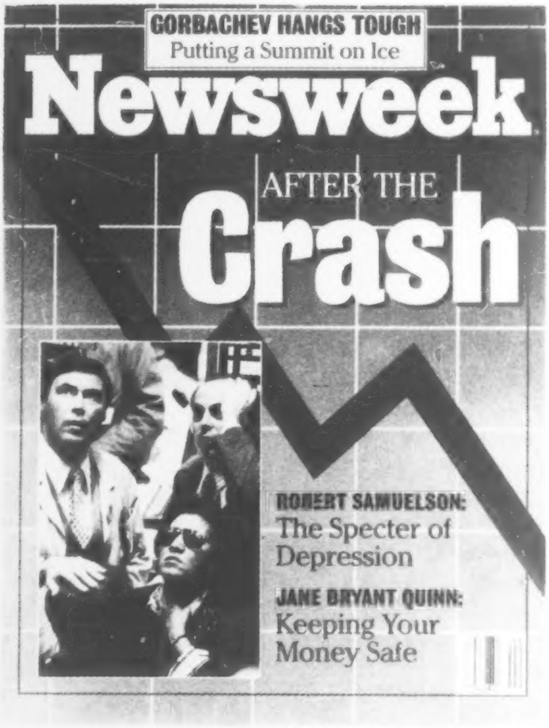
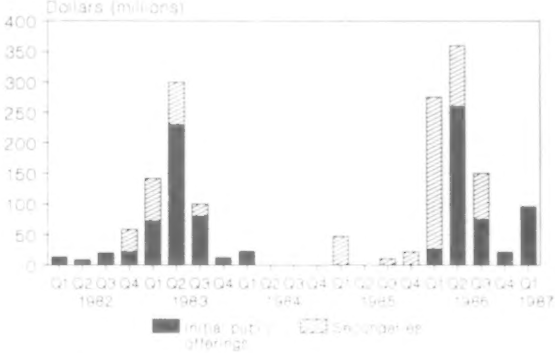


Photo credit: Newsweek, Nov. 2, 1987

Media coverage of the 1987 stock market crash.

Figure 5-4.-Capital Raised in Public Offerings for Biotechnology



SOURCE: Adapted from Russell Ray, Alex. Brown & Sons, 1987

nearly equal amount still registered with the Securities and Exchange Commission (17). Biotechnology continues to boast the highest price to earnings ratio of any industry (21).

Companies focusing on human therapeutics tend to have the most public stock offerings, whereas companies involved in diagnostics, reagents, animal agriculture, and specialty chemicals have not gone public at the same rate. In 1987, however, five of the eight biotechnology companies making initial public offerings emphasized agriculture (17).

The market valuation for biotechnology prior to October 19, 1987 was $9 billion to $10 billion, excluding any participation by companies with diverse businesses, such as large drug or chemical companies. Three to four billion of the total market valuation went to Genentech alone. A new wave of second and third offerings swept Wall Street in 1986 and early 1987 as some of the more mature firms financed production scale-ups and clinical trials. Fifteen companies returned to the public market in 1986, raising another $390 million (15) (see figure 5-4).

In 1986, stocks appreciated in value 60 percent on average and in 1987, stock climbed another 50 percent in price (25). Approval of new products as well as the presence of takeover bidders, helped precipitate these gains. However, analysts estimate that the stock market crash of October 1987 devalued biotechnology companies by 40 to 60 percent on average, reducing total industry market capitalism to about $4.5 billion. Less flexible venture capital markets are likely to hurt biotechnology companies because of their capital intensive, cash consuming nature.

Despite the ability of biotechnology firms to raise capital, industry losses totaled $70 million in 1985 and approached $450 million in 1986. Even Genentech at $60 per share reported earnings of only $0.18 per share in 1986. Unlike other industrial sectors, biotechnology is dominated by a few firms: those able to withstand the consolidation that occurred between 1983 and 1986. Genentech has dominated in terms of industry revenues (30 percent), market capitalization (50 percent), and property, plant, and equipment invested in by the independent firms (30 percent) (25). In 1987, when Genentech initially failed to receive FDA approval for tissue-plasminogen activator (tPA), more than 14 million shares changed hands in a single day, with its stock plunging $11.50 a share to $36.75.

The financial activity surrounding biotechnology depends heavily on the successes and failures of the frontrunners.

The status of a company's product in the regulatory process at FDA will continue to affect stock activity as concerned investors take profits. When approval is granted expeditiously, the biotechnology group gains. If approval is delayed, stock prices slide. Meaningful operating profits will eventually be reliable indicators of a company's potential profitability, but for most, it is still an illusory concept.

Some analysts contend that Wall Street has created a false high through hype and overpromotion of "star" companies or products. In August 1986, Endotronics, a Minnesota-based biotechnology company, closed at its all-time high of $35.50 a share—130 times the company's projected earnings. Eight months later it traded at 75 cents. In April 1987, it filed for bankruptcy. Critics and company stockholders contend that the company was fueled more by its promotion that its potential (31).

In addition, most public stock offerings have been by pharmaceutically based DBCs. Analysts are predicting more initial public offerings in the agricultural field (19). **Given the uncertain regulatory climate prevalent in crop and related microbial biotechnology, regulatory delays could have a significant effect on stock prices.**

Finally, the bull market that has existed since 1982 has served all biotechnology well. In a bear market, all but the top ten firms may have to face serious constrictions on the availability of capital through the public markets. As Richard Bock writes (4):

> With the first products just coming on the market, it's obvious that biotech shares are not selling due to earnings, sales, or the payout of dividends. . . . Financial fundamentals **eventually** will be important in weighing the worth of biotech companies, but they are not at this juncture. Analysis based on financial results alone could lower biotech stock prices and kill the goose that cloned the golden egg right in the middle of Wall Street.

Debt Financing

As companies mature, debt financing has become an available means of financing without giving up equity. A survey of firms conducted by Arthur Young found that 13 percent of the larger companies made use of bank borrowings as compared to 3 percent of the small firms (39). Genentech, Cetus, and Bio-Technology General have turned to convertible debt financing in the past year. DBCs may also raise capital on interest from short-term loans and industrial revenue bonds.

Debt financing is a sign of maturity for some firms. Because the company is obliged to service the debt almost immediately, it must be in the position of having products nearly ready for marketing. It is not a desirable method of financing for companies still requiring high cash flows for R&D.

COLLABORATIVE VENTURES IN BIOTECHNOLOGY

Despite the predominance of a few companies, more than 400 dedicated U.S. biotechnology companies remain in business operating at annual losses. Alliances between DBCs and between DBCs and large diversified corporations have become an important source of funds as alternative sources become more conservative. Wall Street relies on corporate alliances as one indication of the value of the firm (36).

Large, diversified corporations increasingly access the potential benefits of these technologies through their own in-house capabilities, or through strategic alliances and acquisitions of DBCs. In addition, large corporations are better able to withstand the prolonged approval and marketing processes inevitable in the final stages of product development, making alliances with DBCs to acquire technology.

These collaborative ventures, or strategic alliances, are associations between separate business entities that fall short of a formal merger, but that unite certain agreed upon resources of each entity for a limited purpose. They are an important means for technology transfer: few biotechnology companies can conduct all aspects of R&D from bench to market. Collaborative ventures may involve acquisition, equity purchase, licensing agreements, marketing agreements, research contracts, or joint ventures.

Collaborative ventures have been essential in the development of industrial biotechnology for two reasons:

- They allow small biotechnology-intensive firms to overcome resource limitations which may prevent them from developing or marketing a product themselves. Smaller firms seem to be seeking near-term cash flow to bankroll their projected growth and gain access to the marketing capabilities of large corporations.
- They allow established companies less costly methods to develop expertise in areas in which they lack in-house capability. Benefits for the large firms in such arrangements are primarily access to cutting edge research and highly trained scientists.

Collaborative ventures can create a protective environment for the external commercialization of a DBC's research. The DBC can avoid the problem of having to expose its innovation to a wide range of prospective licensees and can mitigate the appropriability problem by having the licensee pay for some portion of the R&D costs up front. Through equity investments and joint ventures, the DBC can prevent the established firm from opportunistically appropriating rents on the technology through contractual safeguards. Manufacturing and marketing agreements allow the DBC to disclose far fewer scientific or technical details.

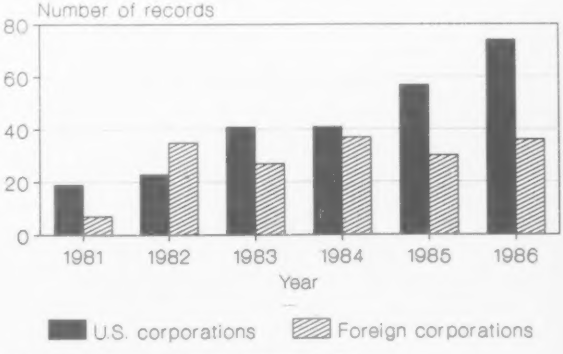
To stay independent, most DBCs are strengthening their alliances with major corporations. Few DBCs have succeeded in becoming full-fledged, fully integrated pharmaceutical or chemical houses, though many aim to do so. Corporate investments in public companies provided the bulk of new capital for biotechnology (approximately $128 million) in the first nine months of 1985 (7). Cumulatively, corporations have provided $2.2 billion or 56 percent of funds for biotechnology through 1985 (27). All indications seem to be that the percentage will increase.

An important difference exists between the collaborative activities of biotechnology firms and the semiconductor firms that emerged in the early stages of that industry. The semiconductor firms of the 1950s did not resort to licensing and joint ventures to commercialize their technology as have biotechnology firms (34). This may be due to the fact that the semiconductor industry was selling largely to the Department of Defense, a market that had much lower marketing and product introduction costs than the markets for new biotechnology products (26).

An OTA review of 552 industrial collaborations between 1981 and 1986 found a steady rise in the number of collaborative ventures. Collecting complete information on the number and nature of collaborations in commercial biotechnology is complicated by the proprietary nature of such information. Companies that are publicly held usually document their collaborative agreements with other industrial firms in their mandatory 10K filings. However, most of the new biotechnology ventures are privately held firms that are under no such requirements. Figure 5-5 illustrates collaborative ventures between U.S. biotechnology companies and between U.S. and foreign companies between 1981 and 1986.

Collaborations are not always between large corporations and small companies, although that is the norm. There are about 800 firms active in bio-

Figure 5-5.-Collaborative Ventures of U.S. Biotechnology Companies, 1981-86



SOURCE: Office of Technology Assessment, 1988.

technology worldwide, with between 1,000 and 1,500 joint venture agreements among them, although it is not known how many of these are strictly research collaborations. An estimated three-quarters of the agreements are between large and small firms and less than one-quarter of the agreements are international collaborations (32).

Research to date suggests that big firms are mostly gaining licenses to market products through these agreements, but not licenses to the technology to manufacture products. Contrary to the belief of many analysts who think that the trend toward such joint venture agreements is on the wane, the number of these agreements is increasing, or at least remaining level (34).

In addition, although there is an increase in the number of collaborative ventures per year, no one type of action (e.g., equity purchase, licensing agreement) has increased. This is true for both U.S./U.S. agreements and U.S./foreign agreements. Table 5-4 displays the number of each type of agreement between U.S. firms and between U.S. and foreign firms between 1981 and 1986. Most records of agreements specify the type of action; where this was not the case, unspecified collaborative ventures were categorized as joint ventures.

Two companies serve as examples of the level of activity generated by strategic alliances—Amgen (pharmaceuticals) and Calgene (agriculture). Amgen's March 1986 secondary offering prospectus listed eight prominent corporate partners: Johnson & Johnson, Kirin Brewery, Abbott Laboratories, SmithKline Beckman, Eastman Kodak, Arbor Acres Farm, Upjohn, and Texaco. Calgene has teamed up with Procter & Gamble, Rhone-Poulenc, Agrochimie, Kemira Oy, Roussel-Uclaf, Ciba-Geigy, Campbell Soup, and Philip Morris (20). One interesting aspect of these alliances is that in both cases, the DBC has managed to negotiate separate agreements with proven competitors.

On the corporate side, many companies have used major licensing strategies to move into biotechnology. Kodak signed nine deals in 1984 with biotechnology start-ups. Kodak has signed research contracts with DBCs to work in areas as diverse as cancer drugs and genetically engineered indigo dye for blue jean manufacturers. Johnson & Johnson owns equity stakes in 11 biotechnology companies. American Cyanamid signed more than 15 licensing agreements with DBCs over the past five years (12).

Most U.S./U.S. collaborative ventures on record are in the area of human therapeutics (29 percent) or clinical diagnostics (25 percent). Most DBCs are working in those areas and the costs of forward integration are high, making joint agreements desirable. Collaborative ventures in therapeutics are largely responsible for overall increases in collaborative actions over the years. It is clearly the area of the most intense business activity.

In one study (34), R&D contracts and R&D marketing agreements accounted for all the collaborative ventures in plant biotechnology. The lack of straight marketing, supply, or technology transfer agreements in the study sample suggests that DBCs in plant biotechnology are not carrying out R&D on their own. Of the 48 plant agriculture product developments listed by Paine Webber, biotechnology companies were acting without a commercial partner in only 8 cases (30). Some assert

Table 5-4.—Collaborations Between U.S. Firms and Between U.S. and Foreign Firms, 1981-86

	U.S./U.S. (U.S./Foreign)						
Type	1981	1982	1983	1984	1985	1986	Total
Joint venture[a]	5 (3)	6 (22)	27 (8)	14 (17)	29 (11)	23 (16)	104 (77)
Equity purchase	8 (1)	7 (6)	3 (1)	8 (2)	9 (2)	13 (4)	48 (16)
Licensing agreement	4 (1)	4 (2)	4 (5)	6 (5)	8 (5)	4 (1)	30 (19)
Marketing agreement	4 (1)	0 (6)	2 (4)	5 (4)	8 (5)	13 (7)	32 (27)
Research contract	1 (2)	6 (3)	7 (1)	6 (3)	6 (5)	15 (4)	41 (18)
Totals	22 (8)	23 (39)	43 (19)	39 (31)	60 (28)	68 (32)	255 (157)

[a] Unspecified collaborations were categorized as joint ventures.

SOURCE: Office of Technology Assessment, 1988.

that biotechnology in plant agriculture is not as commercially advanced as in other sectors, and that in order to fund long-term R&D, agriculture biotechnology companies have had to turn to corporate sponsors. In addition, small companies may rely on large companies for their marketing network in order to reach more farmers (13).

U.S./Foreign Collaborative Ventures

As DBCs near development and production, collaborations with foreign firms provide them access to international markets. While this strengthens the financial position of the DBC, there is some concern that the enhancement of biotechnology in foreign firms reduces the future rent-earning potential of U.S. biotechnology (37). One protection against such a loss is rigorous protection and enforcement of intellectual property and patent rights in the United States.

As shown in figure 5-5, **while the number of collaborative ventures between biotechnology firms has steadily increased, the bulk of the activity has been between U.S. companies rather than with foreign firms**. U.S. biotechnology companies have only two-thirds as many joint actions with foreign corporations as with U.S. corporations. U.S. private investors accounted for 90 percent (or $3.7 billion) of all international biotechnology investment dollars as of 1985 (27). OTA did not collect data on collaborative ventures between foreign firms. However, many collaborations do not involve U.S. firms and biotechnology-based industries are developing in Western Europe, Japan, and South America.

OTA found that 41 percent of U.S./foreign collaborative ventures occurred in human therapeutics, 13 percent in diagnostics, and 9 percent in plant or animal agriculture.

Table 5-5.—Collaborative Ventures Between U.S. Dedicated Biotechnology Companies and Foreign Corporations, 1981-86

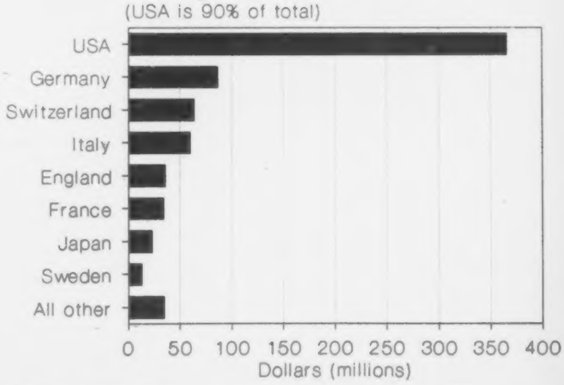
	Year						
Country	1981	1982	1983	1984	1985	1986	Total
Belgium	0	0	0	0	0	2	2
Canada	0	0	0	1	0	0	1
China	0	0	1	0	0	1	2
Denmark	0	1	1	0	0	2	4
France	1	1	0	1	1	2	6
Italy	0	1	0	2	3	1	7
Japan	6	22	12	15	8	8	71
Malaysia	0	1	0	0	0	0	1
Netherlands	0	0	1	1	0	3	5
Sweden	0	2	0	3	5	4	14
Switzerland	1	3	2	9	5	9	29
United Kingdom	0	1	0	2	4	2	9
West Germany	0	3	0	3	6	2	14
Totals	8	35	17	37	32	36	165

SOURCE: Office of Technology Assessment, 1988.

Japanese corporations lead all other countries in the number of collaborations arranged with U.S. biotechnology companies (see table 5-5), but do not lead in amount of private dollars invested. Figure 5-6 displays the cumulative investments of private investors by the United States, and six specific Western European countries. Swiss, Swedish, and West German corporations have been active collaborators with U.S. firms. In fact, collaborations between U.S. and Japanese firms have dropped and leveled off in the past 3 years, whereas collaborations with companies from an increasing number of European countries has increased, suggesting "internationalization" of commerce in biotechnology.

U.S. firms have collaborated with Japanese firms more than any other foreign firms (8). Of the 71 U.S./Japanese collaborations identified between 1981 and 1986, 39 large Japanese corporations, and 43 American firms were involved. The collaborations are overwhelmingly in the application of biotechnology to areas of human health care.

Figure 5-6.-Country of Private Investor Cumulative Investment



SOURCE: Adapted from James R. Murray & Co., Chicago, IL, 1986.

The Vice President for investment banking at Nomura Securities International claims that while most of Japan's biotechnological activity takes place within its established industry, the Japanese pharmaceutical industry has been the last industrial entity to get involved (16). This could explain Japan's heavy involvement with U.S. biotechnology companies. These collaborations provide a number of business opportunities for American firms, including research funding, sponsorship of Japanese clinical trials, and marketing and distribution of products within Japan. Of the collaborations analyzed, Japanese companies are less likely to engage in equity arrangements than U.S. companies collaborating together. In addition, Japanese firms are more likely to arrange a licensing agreement with a U.S. firm and are twice as likely to form a marketing agreement than would be found in U.S./U.S. collaborations. These agreements tend to be smaller dollar-wise, explaining the discrepancy between number of agreements and dollars invested (28). A listing of U.S./Japanese collaborative agreements between 1981 and 1986 appears in table 5-6.

Table 5-6.—U.S./Japanese Joint Actions in Biotechnology, 1981-86

U.S. company	Japanese company	Action	Product
1981			
Biogen	Green Cross	J	vaccine
Collaborative Research	Green Cross	E	urokinase
Enzo	Kinto	J	enzymes
Genentech	Toray Industries	M,R	interferon
Hybritech	Mitsubishi	L	anti-IGE kit
1982			
Bioassay Systems	Toray Industries	M	bioassay
Biogen	Fujisawa	J	tPA
Biogen	Meiji Seika	J	antibiotic
Biogen	Shionogi	J	HSA
Biogen	Teijin	J,M	Factor VIII
Biogen	Yamanouchi	J	anti-inflammatory
Biotech Research Lab	Fujizoki	E,J	MAB
Collaborative Research	Green Cross	M	B-interferon
Enzo	Meiji Seika	L,M	HCG Test
Genentech	Mitsubishi Chemical	J	tPA
Genentech	Takeda	?	B-interferon
Genex	Green Cross	J	HSA
Genex	Mitsui Toatsu	J	urokinase
Genex	Yamanouchi	J	tPA
Hana Biologics	Fujizoki	E,J	diagnostics
Hybritech	Green Cross	J	immunoglobulins
Hybritech	Teijin	J	MABs
Interferon Sciences	Green Cross	J	interferons
Interferon Sciences	Green Cross	M	G-interferon
Monotech Labs	Eken	R	diagnostics
Techniclone	Fujizoki	L	diagnostics
1983			
Biogen	Shionogi	L	IL-2
Biogen	Suntory	J	TNF
Centocor	Toray Industries	J,L	diagnostics
Collaborative Research	Green Cross	L	interferon
Genentech	Daiichi Seiyaku	L	G-interferon
Genentech	Mitsubishi	J	tPA
Genex	Yoshitomi	J	IL-2
Innovax Labs	Snow Brand Milk	L	?
Integrated Genetics	Toyobo	J,M	tPA
Repligen	C. Itoh	E,M	proteins
University Genetics	Nissho Iwai	M	?
Xenogen	Mitsui Toatsu	J	feed additives

(continued on next page)

Table 5-6.—U.S./Japanese Joint Actions in Biotechnology, 1981-86—Continued

U.S. company	Japanese company	Action	Product
1984			
Amgen	Kirin Brewery	J	erythropoietin
Atlantic Antibodies	Oriental Yeast	M	antisera
Battelle Development	Mitsubishi	J	?
Endotronics	Mitsui	M	instrumentation
Genentech	Fujisawa	L,M	lymphotoxin
Genetics Institute	Chugai	J,M	erythropoietin
Integrated Genetics	Fujirebio	J	DNA probe
Human Antibody Tech	Kyowa Hakko	J	diagnostics
Hybritech	Toyo Soda	J,M	diagnostics
Lymphomed	Fujisawa	M	anti-pneumonia
Molecular Biosystems	Funakoshi	M	microspheres
NPI	Sumitomo	J	foods
Plant Genetics	Kirin Brewery	J,E	seed
Queue Systems	Shin Meiwa Industry	M,L	Bt products
Ventrex	Funakoshi	M	MAB
1985			
Applied Biosystems	Japan Scientific	J	reagents
Biogen	Sumitomo	J	colony stimulating factor
Calgene	Kuraray	J	agrichemicals
Collagen	Lederle Japan	L	implants
Genentech	Mitsubishi	L	vaccines
Molecular Genetics	Shionogi	M	veterinary
Unigene Labs	Toyo Soda	L	immunization
1986			
Bioreactor Technologies	C.Itoh	M	bioreactors
Cyanotech	Daikyo Oil Co.	E	?
Diagnostic Products	Dainippon Ink & Chemical	M	immuno-diagnostics
Endotronics	Nippon Chem. Indus.	J	hGH
Genzyme	Nagase & Co.	J	amylase
Ingene	Mitsubishi	J	sweeteners
Liposome Technology	Takeda	R	?
Zymogenetics	Teijin Ltd.	J	blood factors

KEY: E = equity purchase
J = joint venture
L = licensing agreement
M = marketing agreement
R = research contract

SOURCE: Office of Technology Assessment, 1988.

SUMMARY AND CONCLUSIONS

U.S. commercial biotechnology remains healthy and competitive. OTA identified 403 U.S. companies dedicated to biotechnology (DBCs) and 70 large, established U.S. corporations with significant investments in biotechnology. **Combined, U.S. industry devoted about $1.5 to $2.0 billion to biotechnology R&D in 1987.**

The shakeout predicted to occur among dedicated biotechnology companies has not occurred, although the frontrunners have become stronger. Financing is concentrated heavily in a few firms. Methods of financing for DBCs continue to evolve and are heavily dependent on the conditions of financial markets. Despite industry losses and until the stock market decline of October 1987, commercial biotechnology has been able to raise capital. Financial activity depends heavily on the successes and failures of the frontrunners. Meaningful operating profits are not yet reliable indicators of a company's potential profitability. Thus far, many companies have been able to attract financing based on potential alone, but it appears that safe and reliable products and wise marketing strategies will eventually be the safety net for survival. Increasingly, large established companies are playing a critical role in innovative research as well as in the final stages of commercialization of biotechnology products and processes; they are more able to bear the development, regulatory, and marketing costs of commercialization. A few

DBCs have successfully used the benefits of RDLPs to raise capital.

Human health care, primarily therapeutics and diagnostics, continues to be the focus of most biotechnology R&D investments, both by DBCs and major corporations. The sectoral breakdown of the industry has remained fairly constant since OTA last reported on commercial biotechnology in 1984, with chemicals and agriculture ranking second and third as the fields of application of industrial biotechnology. There is evidence, however, that agriculture, plant biotechnology in particular, is a growing field and has begun to attract the attention of the public financial markets. A strong support industry of companies producing reagents, equipment, and customized processes in such areas as cell culture continues to grow and has been successful in generating revenues. Revenues based on products directly derived from biotechnology R&D remain scarce. No reliable data are available on total industry sales of biotechnology products.

Strategic alliances between large corporations and DBCs are on the rise and have become an indicator to Wall Street of the value of a firm. **Although 95 percent of the large corporations investing in biotechnology have in-house capabilities, 83 percent also rely on outside sources of innovation, either DBCs or universities. There appears to be a mutual benefit to these collaborations, and there is no indication that a takeover of biotechnology's potential by corporate interests is imminent.**

While collaborations between U.S. firms are on the rise, collaborations between U.S. firms and foreign firms seems to be declining. There were twice as many collaborations between U.S. companies as between U.S. and foreign companies in 1986. Of those foreign firms collaborating with U.S. companies, the breakdown is more diverse, with Japan playing less of a role and other countries becoming more active.

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Chapter 6

Factors Affecting Commercialization and Innovation in Biotechnology

"No amount of R&D funding can overcome unresolvable bureaucratic obstacles to the testing and use of new biotechnology."

Frank E. Young
FDA Commissioner, 1987

"It's difficult to imagine how biotechnology could be 'controlled.' "

Robert Yuan
International Trade Administration
Department of Commerce
Sept. 15, 1987

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Chapter 6

Factors Affecting Commercialization and Innovation in Biotechnology

INTRODUCTION

Counting dollars spent on biotechnology research is only one way to measure the vigor of commercial biotechnology. Assessing industrial policy is just as useful. Although the concept of a U.S. industrial policy has been around since the New Deal, most recently it returned to the national agenda in 1983 as part of the presidential election campaign. Difficult to define under any circumstances, industrial policy as it relates to biotechnology is nonexistent. However, several factors comprising industrial policy, such as tax rules, antitrust law, trade and export policy, patent law, and the regulatory climate, can be discussed in terms of their effects on biotechnology. The following section describes policies, legal frameworks, and administrative laws affecting commercialization and innovation in biotechnology.

TRADE ISSUES

There is a growing concern in some sectors that pursuing a trade policy that promotes high-technology goods for export compromises our national security objectives. This conflict might impede the export of biotechnology products unless economic and national security interests become balanced. As U.S. biotechnology industries have expanded, attention has focused on international promotion and commercialization. Many believe that high-technology industries, such as those employing biotechnology, might contribute to our economic competitiveness and provide a partial remedy for our current deficit crisis.

However, several aspects of U.S. unilateral controls have the potential to put U.S. biotechnology firms at a competitive disadvantage relative to those of the other members of the Coordinating Committee on Multilateral Export Controls (CoCom). Formed in 1949 to coordinate multilateral trade controls to Soviet bloc countries, CoCom has 16 member nations. Because the biotechnology industries are still developing, it is difficult to discern exactly how much of an effect these export controls and barriers to trade will actually have.

Export Controls

Export controls can impede export transactions. They restrict international technology transfer for national security, foreign policy, or short supply reasons. The National Academy of Sciences (NAS) recently estimated that in 1985, export controls cost the U.S. economy approximately $9.3 billion (24). The debate is composed of proponents who believe that relaxing export controls would increase the accessibility of Western technology for the Soviets and opponents that believe excessive controls harm U.S. economic competitiveness and trade relations (5). In the case of biotechnology exports, some argue that unrestrained export will enhance the ability of other nations to produce biological warfare agents.

Mechanisms of Control

Controls for biotechnology exports come primarily under the jurisdiction of the Food and Drug Administration (FDA), the Department of Commerce (DOC), and the Department of Defense (DoD). Different statutes may apply to the exportation of a biotechnology product—the FDA's Federal Food, Drug, and Cosmetics Act (FFDCA) and its Drug Export Amendments Act (Public Law 99-660), the DOC's Export Administration Act (EAA) (Public Law 96-72) and its amendments, and the Export Administration Act Amendments of 1985 (EAAA) (Public Law 99-64). Other agencies, such as the U.S. Department of Agriculture (USDA) or the State Department, may be asked to review potential decisions, but have no direct regulatory power under these statutes.

FDA Approval

Since the passage of the Drug Export Amendments Act of 1986 (Public Law 99-660), FDA approval is no longer a necessary requirement for exportation of drugs and biological products. These amendments abolished the law requiring FDA approval prior to exporting, giving U.S. biotechnology companies greater access to the international market. Before this law was passed, the companies either licensed their technology to foreign manufacturers, established foreign manufacturing facilities, or lost the business abroad. The path has been cleared substantially, though the FDA still must approve the export request, and with few exceptions, the product can only be exported to those countries that are on a list of 21 countries specified in the Act and that have already approved the drug. Furthermore, the exporter must have a written agreement from each importer stating that the importer will not export the drug to any countries that do not appear on the list of 21 countries (15). The export license is subject to cancellation if the FDA finds that the company is not actively pursuing approval. (See ch. 9 for further discussion.)

DOC Oversight

DOC plays a large role in the export control process through its licensing system. Its activities in export control are guided by U.S. foreign policy, national security, or supply issues. In the case of biotechnology, attention will most likely be focused on exports perceived as threats to U.S. national security (15). The DOC follows the procedures contained in the 600-page Export Administration Regulations (24). Many products and technologies require only a general license, and need no application to be exported. Referral to the Commodity Control List (CCL) is necessary for a biotechnology company to determine whether it needs to apply for a validated license for its product, and if so, what type. The CCL is published by the DOC and administered by the DOC's Bureau of Export Administration. It divides goods and technologies into categories and also into geographic groups according to a country's level of control. Controlled commodities on the unclassified list are categorized into 10 groups; groups 7 and 9 pertain to biotechnology. Group 7 is primarily chemical compounds with a subgroup that includes DNA, culture media, pharmaceutical products, proteins, and nucleotides; group 9 includes microorganisms, viruses, bacteria, fungi, and protozoa.

If an item or technical data are included in one of the categories of the CCL and there is evidence that it is available abroad, it is necessary for the DOC's Office of Foreign Availability to conduct an assessment. If the item is available in sufficient quantities and is of comparable quality, the item is supposed to be decontrolled. However, if after a positive determination the President believes that decontrol will threaten national security objectives, a "national security override" may be enacted (25). Attempts may then be made through negotiation to persuade the foreign sources to enact controls to eliminate the foreign availability (7). Once the determination is made, the results are published within 30 days in the *Federal Register* (25).

DoD Oversight

DoD oversees products and technologies that appear on the Militarily Critical Technologies List (MCTL). Unlike the CCL, the MCTL is not a control list; rather it provides a technical basis and guidance for DOC export decisions on technology and equipment that may be used in military systems (24,36). The unclassified MCTL contains four parts—arrays of know-how; keystone manufacturing, inspection and test equipment; keystone materials; and goods which could reveal know-how relevant to the U.S. military system (36). It includes biotechnology products that have dual-use status—products with both civilian and military applications. For example, bioreactors or high-capacity separating devices are dual-use technologies because, in addition to their positive applications, they can also be used to produce biological warfare agents (3). One of the categories with direct relevance to biotechnology covers know-how for recombinant DNA and bioprocessing technologies.

Due to the limited number of biotechnology products on the market at this time, it is difficult to predict how the DOC will interpret the sections of the MCTL relevant to biotechnology. In addition to its role in export controls, the DoD also has oversight in the patent law process. The Department is entitled to screen applications and can request the DOC to impose secrecy orders on patents, causing them to become classified information.

Effects of Controls

Since the 1984 OTA report *Commercial Biotechnology: An International Analysis*, was published, there has been little substantive change in export controls and trade issues as they relate to biotechnology. However, with more products available, the DOC will be more taxed regarding licensing applications. According to some industry representatives, current export policies disregard the interests of biotechnology firms, and are not always administered consistently (12). The prevailing view in industrial circles concerned with export control in biotechnology is that the issues are worse now than they were before the 1985 Amendments were passed. Some suggest that the agencies involved are inadequately staffed and poorly trained to deal with the complexity presented by biotechnology and other high-technology areas.

The DOC underwent a reorganization after the passage of the EAAA. Issues of export control are now handled in a newly created entity of the DOC. The Bureau of Export Administration now has its own Under Secretary and is no longer housed under the International Trade Administration (ITA). The previous position of Export Administration raised conflict of interest questions because the ITA was involved with both the promotion and the control of exports. The new level of Export Administration gives more visibility to the export control issues.

The decontrol of technologies on the CCL has proved to be a contentious issue. If the DOC's Office of Foreign Availability conducts an assessment and determines that an item is available abroad, then that item is supposed to be decontrolled. A recent NAS study concluded that the technology decontrol process has not been carried out effectively. NAS attributed this to the lack of time constraints in the legislation and the excessive influence of the DoD. It was also recommended that the in-house technical and analytical expertise of the DOC be upgraded, particularly in the areas of high-technology products and processes (24).

However, the DOC has not been totally ignorant of industry needs. In 1986, DOC responded to criticisms that the controls were retarding West-West trade, by introducing a certified end user or "gold-card" status to approved, reliable companies in Japan and 14 European nations (24,7). These 2-year licenses speed up the export process by eliminating the need for repeated applications for export licenses to those buyers. Whether this provision is as useful to high-technology goods exporters as originally predicted remains to be seen.

In addition, under the direction of the DOC's Bureau of Export Administration, a Technical Advisory Committee (TAC) met in April of 1985 for the first time. Similar TACs exist to advise on issues in computer systems, electronic instrumentation, semiconductors, telecommunications, and transportation. The Biotechnology TAC includes both biotechnology industrialists and government representatives from the DOC, DoD, and State Department. Members are nominated to TAC and serve 4-year terms of office. They provide information and advice to participating agencies on technical matters, export regulations affecting biotechnology, issues of trade development as affected by the controls, worldwide availability, and new technological developments. However, the TAC was not set up to provide members of the biotechnology industries with information about the export control process (11). It is not clear that the goals of TAC have been met, particularly in the decontrol of items available abroad. At a September 1987 meeting of the TAC, members expressed some concern about the productivity of their efforts.

Due to expire in September of 1989, the EAA is again being discussed in Congress. The issue that remains is whether it is possible for Congress to formulate a policy that balances U.S. foreign policy and national security interests while pursuing national economic vitality. The outcome of this debate is important to the future success of the biotechnology industries, because they may be placed at a competitive disadvantage relative to nations without unilateral controls. **The economic potential of the biotechnology industries may never be realized if companies cannot comply with the procedures and restrictions associated with the Export Administration Regulations** (12). Under review are several aspects of the legislative proposals that apply to biotechnology. These are:

- outlining the specific functions of the government agencies involved in the export control process, thereby clarifying the DoD's role;
- removing controls (licensing requirements) on low-technology items;
- developing and enforcing timelines for decontrolling items that have been found outside the United States by the DOC's Office of Foreign Availability; and
- reviewing the Commodity Control List with the intention of reducing its size (17).

Other Barriers

Other trade barriers also affect biotechnology products. Actual tariffs on products are rare. Nontariff barriers, defined as "any government intervention affecting competition between imported and domestic goods" (33), are most likely to present obstacles for U.S. biotechnology products abroad. The barriers to biotechnology transfer that were identified in the 1984 OTA report remain. These are standards and certification systems, subsidies, price regulation, and government procurement. All are methods to protect a product's domestic market.

REGULATORY CONCERNS

In a report prepared for the Environmental Protection Agency (8), market considerations were cited as dominant factors influencing industrial biotechnology R&D strategies. However, the status of governmental regulation can become a primary factor by affecting the cost, time to market, and especially the uncertainty of R&D. Thus, when regulation is untried in the marketplace, untested in the courts, or ambiguous in status and scope, the resulting set of uncertainties can become a dominant influence in selecting or rejecting an R&D objective and associated business strategies.

Multiple tensions among uncertainty, market potential, and the economic factors of production can affect research, production, and marketing decisions in many significant ways. Because the range of commercial opportunities for biotechnology is uncommonly wide, regulatory uncertainty could be a factor driving firms away from applications in areas of high uncertainty to those of lesser uncertainty.

Interviews with a number of senior executives in biotechnology firms revealed that a substantial majority of them see regulatory uncertainty as being among their most pressing problems, including specifically the increased cost of performing R&D and doing business generally. The General Accounting Office (GAO) has noted that regulatory requirements vary considerably by product type and by the agency charged with regulatory responsibilities. Each agency employs its own internally defined standards and procedures (32).

While the regulatory aspects of biotechnology are covered in *Field Testing Engineered Organisms: Genetic and Ecological Issues* (34), it is important to underscore the relationship of several of these to private R&D costs and investment in biotechnology. Analysis of a variety of reports and interviews with key individuals in and out of government leads to a major conclusion: from an industry perspective, regulatory uncertainty looms as a critical factor in the future of biotechnology. **It is likely that biotechnology faces a much different and more stringent regulatory environment than do many other components of**

Photo credit: Monsanto

Genetically engineered tomato plants are shown being planted by researchers at a Monsanto-based farm in Jersey County, Illinois.

high-technology industries, increasing the cost of R&D and the amount of total investment required. In addition, the regulatory framework encompasses several agencies, each with its own approach to approval. At present, uncertainties are being resolved and ambiguities identified. It is too early to assess the effects of regulation on commercialization of biotechnology.

The international features of biotechnology regulation will present additional uncertainties. Proposals to establish an international set of guidelines under the auspices of the Organization for Economic Cooperation and Development (OECD) have not been successful. Three U.N. organizations—the U.N. Industrial Development Organization, the World Health Organization, and the U.N. Environment Program—have launched a program to establish new safety guidelines for the infant biotechnology industry in the Third World. Minimum safety guidelines for biotechnology are intended for eventual adoption by *all* countries (19). Biotechnology firms are warily watching the unfolding of regulatory decisions in Europe, Japan, and the United States (38,28).

Industry representatives told OTA that biotechnology progress will be hindered unless the Federal Government pays a great deal more attention to the regulatory arena, especially to risk assessment activities and programs. Former EPA Administrator William Ruckelshaus has put this directly:

> The Administration must attach a high enough value to maintaining our worldwide lead in this technology to devote enough government resources to its regulation so that real public concerns about risks can be satisfied. And that level of attention has not yet been evident from this Administration (23).

Regulatory issues specific to applications of biotechnology in human therapeutics, plant agriculture, and waste use and pollution control are discussed in chapters 9, 10, and 11.

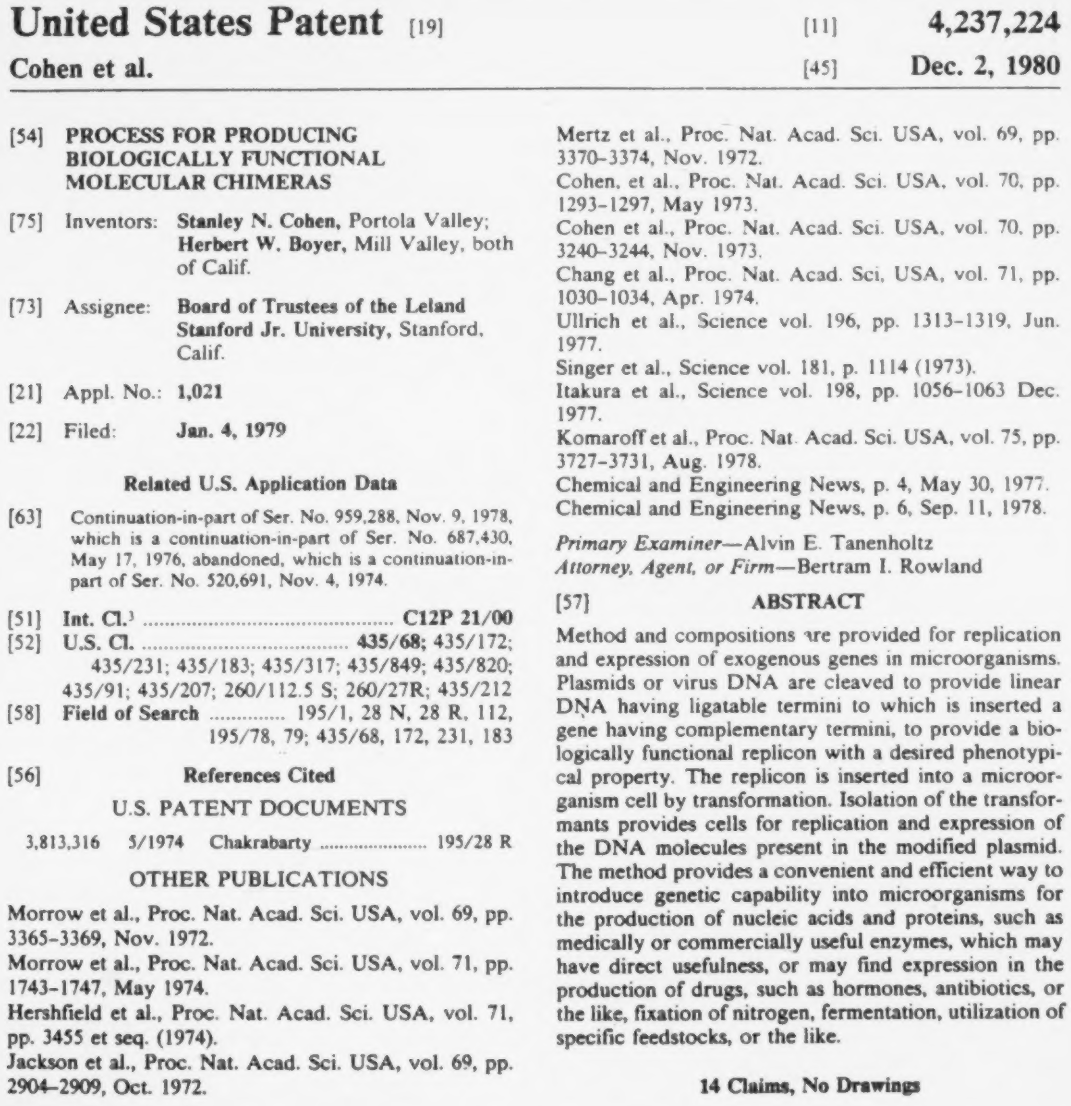
PATENTS AND INVESTMENT

When the Supreme Court addressed the issue of patenting living organisms in *Diamond v. Chakrabarty* in 1980, the potential profitability of biotechnology became apparent to scientists and investors. Since then, 6,000 biotechnology patents have been filed with the the U.S. Patent and Trademark Office (PTO) (37). The tangle of patents awaiting approval is one of the more difficult dilemmas facing the industry today as more and more products near the market. Already, patent battles are being fought over interleukin-2, tissue plasminogen activator, human growth hormone, hybridoma technology, alpha interferon, factor VIII, and use of dual monoclonal antibody sandwich immunoassays in diagnostic test kits. There is significant uncertainty about how the courts will interpret the claims for biotechnology patents. Companies receiving basic product patents are in court enforcing their rights against infringement or defending the patent grant in opposition or revocation proceedings. It is likely that patent litigation in biotechnology will increase given the complex web of partially overlapping patent claims, the high-value products, the problem of prior publication, and the fact that many companies are chasing the same products. Many companies are finding it essential to determine a product's patent position prior to marketing (2). Chapter 9 discusses some of the difficult patent issues facing the human therapeutics industry.

This report does not attempt to assess the complexities of these disputes. An upcoming OTA report on *Patenting Life* will address legal issues in greater detail. It is important to note, however, that patent uncertainty is a critical factor affecting commercialization in biotechnology. Companies face a battle on two fronts: domestic and international. The protection of U.S. patents abroad is currently being pursued by U.S. representatives of the General Agreement on Tariffs and Trade (31).

Investors watch the biotechnology patent battles and often react quickly to the latest legal decision. For example, in September 1986, Genentech's stock dropped 10.5 points following the

The patent awarded to Stanley Cohen and Herbert Boyer in 1980. This patent has since become Stanford University's top earning patent ($1.7 million annually).



United States Patent [19]

Cohen et al.

[11] **4,237,224**

[45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Portola Valley; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University**, Stanford, Calif.

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] **Int. Cl.**^{3} **C12P 21/00**
[52] **U.S. Cl.** .... **435/68**; 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212
[58] **Field of Search** .... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

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Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

SOURCE: Office of Technology Licensing, Stanford University.

news that Hoffman-La Roche had sued it for infringing a patent for human growth hormone. Genentech's stock rose the previous year when it sued Burroughs-Wellcome (PLC) for allegedly infringing a British patent on tissue plasminogen activator.

On average, DBCs have filed fewer biotechnology patent applications than larger, established firms—1.5 versus 10 applications in 1986. This is most likely due to a greater institutional capacity to file multiple patents in the larger, more diversified companies.

How the courts uphold issued patents, and interpret new ones, as well as how well U.S. companies are able to protect patents abroad, will be issues facing biotechnology forerunners in the next few years. **Uncertainty over patent protection is likely to be costly and will undoubtedly influence the R&D strategy of many companies.** In the short term, trade secrets are being sought as an alternative route for the protection of products. Eighty-five percent of the large corporations responding to the OTA survey indicated that they expect to pursue trade secrecy protection for biotechnology lines in addition to patent protection. While there is no time limit on trade secret protection, disclosure terminates protection. In addition, where parallel research is underway, there is a high likelihood of simultaneous invention, presenting a threat to trade secrecy. While biotechnology industrialists are skeptical about the value of trade secrecy versus patents, the former could be an option where inventions simply are not patentable because they fail to meet the statutory criteria of novelty, non-obviousness, and utility. Trade secrecy is probably more likely to be employed for invented *processes* rather than for *products* (26). Ultimately, patent protection facilitates licensing transactions and is more desirable for many DBCs (22).

Patent and Trademark Office

At the PTO, the Biotechnology and Organic Chemistry group has experienced a turnover of and a difficulty in acquiring patent examiners with expertise in fields associated with biotechnology (see table 6-1). Under these circumstances, it is about 24 months, on the average, before processing of a biotechnology patent application is initiated. In contrast, 6 months is the average time that passes before examination of patent applications for conventional drugs begins (37). **This time lag, along with an atmosphere of general uncertainty over patent rights, may cause companies developing biotechnology products to file many more patents than are typical for conventional drugs.**

There are two reasons why government personnel reviewing drug marketing approval or patent applications become dissatisfied with their positions. First, the work tends to be repetitive and administrative, a disincentive for trained scientists used to more interesting and creative work. Second, these individuals are often capable of earning substantially higher salaries in the private sector. In a rapidly evolving technology such as biotechnology, the industrial regulatory affairs and legal offices (among others) can profit greatly from the "insider's view" of personnel trained at Federal agencies. **Federal incentive programs for trained scientists that will bring them to and keep them at these types of positions in government are vital to the impact of biotechnology on drug development, as well as to other major areas of applied biotechnology.** The PTO is currently undergoing a reorganization of those groups dealing with biotechnology products that is expected to reduce the time lag for patent approvals.

Table 6-1.—Biotechnology Staff and Workload Trends in the U.S. Patent and Trademark Office, 1985-88

	As of Jan. 1988	As of Jan. 1987	As of Jan. 1986	As of Jan. 1985
Examiners	42	32	30	30
Pending applications				
New (not yet acted on)	4,051	3,307	3,155	2,202
Tentatively rejected	2,472	1,879	2,173	1,529
Amended	384	651	445	172
Total	6,907	5,837	5,773	3,903
Total completed (granted or abandoned in previous year)	2,190	2,044	1,573	1,171
Approved applications (previous year)	887	816	712	556
Percent approved	40.5%	40%	45.3%	47.5%

SOURCE: Charles Van Horn, U.S. Patent and Trademark Office, 1987.

ANTITRUST CONSIDERATIONS

OTA was unable to identify antitrust law issues or difficulties unique to biotechnology. The larger debate on antitrust essentially concerns economic policy and high technology in the framework of global competition. However, as was suggested in an earlier OTA report (33), two issues should be raised with respect to biotechnology:

- whether U.S. antitrust law discourages or inhibits formation of R&D joint ventures, thereby retarding innovation and the competitiveness of U.S. firms in world markets; and
- whether U.S. antitrust law inhibits the legitimate exploitation via licensing arrangements of the technology created by R&D efforts.

American companies have traditionally avoided collaboration in R&D. The principle reasons seem to arise from the view that cooperation does not result in benefits, an unwillingness to share proprietary data and decisionmaking, and fears of private or government antitrust actions. But global competition and the rising costs of performing R&D are driving some major U.S. corporations to consider alternatives to internally generated and financed research projects. In biotechnology, a group of companies interested in forming a consortium to conduct research in protein engineering has met to develop plans and raise funds (18).

Since 1980, and especially since passage of the National Cooperative Research Act of 1984 (NCRA) (Public Law 98-462), research consortia have begun to proliferate in various industrial sectors, especially in microelectronics (14). Both the Departments of Commerce and Justice have promoted and encouraged the formation of research consortia to cope with foreign competition. However, the breadth and vagueness of the antitrust statutes, along with perceived ambiguity in the guidelines and business review procedures used by the Justice Department, have resulted in widely held beliefs that collaborative research organizations would be threatened by antitrust actions (27).

Despite underlying suspicion by industry, the Justice Department has never challenged a pure research joint venture under the antitrust law. Between 1950 and 1980, only three joint R&D ventures were challenged, and each involved significant collateral restrictions that were deemed to retard innovation (13). Further, no plaintiff has ever won an antitrust case against a member of a collective research effort (39).

The NCRA was aimed to reduce uncertainty and the level of risks associated with antitrust. It specifically removed the threat of treble damages and made it costly to file frivolous private antitrust actions. Further, NCRA makes it clear that a rule-of-reason analysis will be used to assess the competitive effects of any R&D joint venture. The rule-of-reason concept is important because it means that the licensing practices of an R&D joint venture cannot be automatically condemned under the so called *per se* illegal doctrine, but must be weighed in terms of competitive benefits and any adverse competitive effects. Only those practices found on balance to be anticompetitive could be subject to enforcement action or judicial decree.

Response to NCRA seems positive. The DOC has reported that notifications of new R&D consortia have been taking place at the rate of two or three per month. OTA was informed of only one proposed consortium in biotechnology (18). Consortial activity in biotechnology may be limited for the following reasons.

- Biotechnology is in an early and highly competitive stage, in which patentable processes and know-how are of great importance.
- R&D Limited Partnerships have offered biotechnology firms substantial resources as an alternative to R&D consortia.
- Biotechnology is characterized by rapid technological change, high growth, and private companies with intensive internal R&D activities. The need for widespread collective activities may just be emerging (14).

TAXES AND INVESTMENT

High-technology industries, such as biotechnology, are often characterized bv higher levels of R&D investment than other industries. Tax relief is one of the methods the Federal Government uses to reduce the financial burden on R&D-intensive industries. This is based on the premise that such investment results in public benefits and in a greater rate of industrial innovation than would have occurred otherwise (1). Biotechnology industries rely on tax incentives because of the high levels of R&D necessary to develop and commercialize products. At present, it is difficult to assess the extent to which commercialization and development decisions in the biotechnology industries have been affected by the Tax Reform Act of 1986 (TRA) (Public Law 99-514). The difficulty is due, in part, to the small number of biotechnology companies that are realizing a profit. As more products reach the marketplace, tax planning will become a higher priority for them (6). Some analysts maintain that the revised tax incentives have only affected the distribution of investment, not the total amount of money available for investment (21). For example, RDLPs were originally predicted to disappear because the TRA virtually abolished tax shelters. Yet interest in RDLPs has prevailed. Perhaps this is because they no longer advertise themselves as tax shelters, rather they now emphasize their ability to produce income for the limited partner.

Theories on the effect of the TRA on business investment are abundant. Many in the business community believe that their tax burden has been increased to offset lowered individual tax rates. The TRA altered several of the investment incentives that were adopted under the Economic Recovery Act of 1981 (ERTA) (Public Law 97-34). An aim of TRA was to "level the playing field" for investment, thus creating a more efficient and equitable system (29). Several tax analysts have concluded that high-technology industries were not affected as much as some other industrial sectors. The initial predictions of disaster for the biotechnology industries resulting from TRA have abated.

Capital Gains

One of the most significant impacts of the TRA on the biotechnology industries is its effect on the preferential treatment of capital gains. Prior to the TRA of 1986, gains from selling stocks were preferred over the actual stock dividends. If an asset had been held for 6 months or longer, 60 percent of the gain was not taxed (30). Long-term gains were those held for more than 6 months. Under TRA, the distinction between long- and short-term tax gains was abolished at the end of 1987. Gains and income are now taxed at the same rate.

This is important to investment in the biotechnology industries because the tax treatment of capital gains was a primary attraction for investors in both RDLPs and venture capital companies. Because the returns from venture capital are mostly in the form of capital gains, some see the venture capital method of funding becoming unpopular to investors. For example, under the old treatment of capital gains, 60 percent of long-term gains from the sale of capital assets were not taxed. The remaining 40 percent were taxed at ordinary rates, which did not exceed 50 percent. This meant that the maximum tax on capital gains was 20 percent, compared to the 50 percent maximum rate on ordinary income (4).

Stock Incentive Option

Prior to TRA, it was common for biotechnology companies to offer their employees incentive stock options. **This was beneficial to the employee because the gains on stock options were treated as capital gains rather than ordinary income. Because TRA now taxes any gains received from the sale of stocks as ordinary income, the benefits and the attractiveness of incentive stock options have been reduced.**

In a 1987 workshop held by the Industrial Biotechnology Association, biotechnology industrialists were given ideas on how to restructure their employee incentive programs. Incentive programs have been important for attracting top employees to small biotechnology companies. Since smaller companies cannot compete with the large corporations in salaries, they had offered considerable incentive option packages. It is now recommended that biotechnology companies offer either cash compensation or non-qualified stock

Public Law 99-514
99th Congress

An Act

To reform the internal revenue laws of the United States.

Oct. 22, 1986
[H.R. 3838]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Tax Reform Act of 1986.
26 USC 1 *et seq.*

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) Short Title.—This Act may be cited as the "Tax Reform Act of 1986".

(b) Table of Contents.—

TITLE I—INDIVIDUAL INCOME TAX PROVISIONS

Subtitle A—Rate Reductions; Increase in Standard Deduction and Personal Exemptions

Sec. 101. Rate reductions.
Sec. 102. Increase in standard deduction.
Sec. 103. Increase in personal exemptions.
Sec. 104. Technical amendments.

Subtitle B—Provisions Related to Tax Credits

Sec. 111. Increase in earned income credit.
Sec. 112. Repeal of credit for contributions to candidates for public office.

Subtitle C—Provisions Related to Exclusions

Sec. 121. Taxation of unemployment compensation.
Sec. 122. Prizes and awards.
Sec. 123. Scholarships.

Subtitle D—Provisions Related to Deductions

Sec. 131. Repeal of deduction for 2-earner married couples.
Sec. 132. 2-percent floor on miscellaneous itemized deductions.
Sec. 133. Medical expense deduction limitation increased.
Sec. 134. Repeal of deduction for State and local sales tax.
Sec. 135. Repeal of deduction for adoption expenses.

Subtitle E—Miscellaneous Provisions

Sec. 141. Repeal of income averaging.
Sec. 142. Limitations on deductions for meals, travel, and entertainment.
Sec. 143. Changes in treatment of hobby loss, etc.
Sec. 144. Deduction for mortgage interest and real property taxes allowable where parsonage allowance or military housing allowance received.

Subtitle F—Effective Dates

Sec. 151. Effective dates.

TITLE II—PROVISIONS RELATING TO CAPITAL COST

Subtitle A—Depreciation Provisions

Sec. 201. Modification of accelerated cost recovery system.
Sec. 202. Expensing of depreciable assets.
Sec. 203. Effective dates; general transitional rules.

Subtitle B—Repeal of Regular Investment Tax Credit

Sec. 211. Repeal of regular investment tax credit.
Sec. 212. Effective 15-year carryback of existing carryforwards of steel companies.
Sec. 213. Effective 15-year carryback of existing carryforwards of qualified farmers.

options. These options can be deducted by the company when sold (6).

R&D Tax Credit

The original R&D credit was first adopted under ERTA at a 25 percent incremental rate. It expired at the end of 1985, and was extended for 3 years under TRA at the lower level of 20 percent. In response to criticisms that the definition of "qualified research" had caused companies to reclassify some expenditures as R&D, Congress narrowed the definition to exclude non-research activities. Under TRA, "qualified research" must be "technological in nature" (not social science) and its applications must be useful to the taxpayer in the development of a new or improved business component (20). The R&D credit's definition now places greater emphasis on innovation in research.

The provisions provide a 20 percent credit in excess of the average amount of R&D expenditures for the previous 3 years. The incremental nature of the credit ties it to increasing research expenditures rather than total expenditures made in a year, thus encouraging companies to increase their R&D commitment. Qualifying expenditures include in-house expenditures for R&D wages and supplies and 65 percent of the amount paid for contract research. Equipment expenditures do not qualify. **The R&D tax credit has been of little use to many biotechnology companies because they are not profitable enough to generate a credit.**

The credit will expire again at the end of 1988, and Congress will have to decide whether to continue extending it or to make it a permanent part of the U.S. Tax Code. Those in favor of the credit's permanency are also requesting a restored rate of 25 percent, arguing that the temporary status of the credit reduces its reliability to R&D planners.

Basic Research Tax Credit

The basic research credit was adopted under TRA to encourage and increase spending on basic research at universities and other nonprofit scientific and grant research institutions by businesses. The credit allows companies to deduct 20 percent for research grants, contributions, and contracts under written agreement at universities or nonprofit institutions. Equipment and services for basic research are not included under this credit; only cash funding will be eligible (20). This credit differs from the R&D tax credit in that it is not tied to increased spending levels, but can be applied to the total sum of contract payments. Provided that the payments exceed the fixed minimum base level, a company engaged in multiyear research contracts can take the credit each year (10). The fixed minimum base level is referred to as the "qualified organization base period amount" and is comprised of a maintenance of effort amount plus one percent of the company's average annual research.

Basic research that is eligible for this credit is not eligible for the R&D tax credit. However, basic research that is not claimed under the credit because it does not exceed the qualified organization base period amount, can be taken under the R&D credit as contract expenses. This credit will expire along with the R&D tax credit at the end of 1988, at which time a decision will be made on its impermanent status. While opponents argue that these credits add to the federal budget deficit through revenue loss, proponents cite the benefits to the economy of enhanced cooperation between private industry and universities.

Investment Tax Credit

First instituted in 1962, the investment tax credit (ITC) was one of the specific tax incentives that the Federal Government established to encourage investment in physical plants and equipment. It allowed a company to deduct a 10 percent credit for the cost of qualified property that was either constructed or purchased.

The repeal of the ITC will adversely affect future investment in equipment. The ITC provided a considerable financial advantage to companies and was particularly helpful for start-up companies with large equipment investments. Some financial analysts believe that reduced tax rates for corporations were supposed to compensate for the repeal of the ITC. Lowering the tax rate benefits those companies large enough to qualify, but does little to help small biotechnology companies with little or no profit. Effective tax rates in areas related to technological innovation and R&D investment will be increased by these provisions (36). and may negatively affect the biotechnology industries over time.

Expensing and Depreciation

Another area that was targeted by tax reformers was depreciable assets. Before TRA, deductions for depreciable assets like equipment were often taken before the assets depreciated. However, under the new tax law depreciation rates were slowed down for most assets, reducing the value of the depreciation deduction from a company's taxable income. When combined with the repealed ITC, the TRA may have actually increased the tax burden for equipment investment (6,9). One option used by small businesses is not to take the depreciation and instead take a tax deduction in that year, called expensing, for equipment purchases. In a study on the effects of TRA on technological innovation, the Congressional Research Service called the expensing of intangible costs the most important tax incentive for R&D spending (16). Intangible costs are things such as salaries, supplies, R&D, and marketing; tangible costs usually refer to equipment and buildings.

SUMMARY

Issues of export controls and national security continue to concern some biotechnology industrialists pursuing international markets. The Drug Export Amendments Act of 1986 is seen as a means of assisting biotechnology companies in gaining access to foreign markets. The ultimate impact of these amendments has yet to be determined. Currently, the Department of Commerce and the Department of Defense are examining the roles of the Commodity Control List and the Militarily Critical Technologies List on high-technology exports, including biotechnology products. **As biotechnology produces more products for exportation, industry is concerned that the licensure process will slow to the detriment of U.S. industry.**

Biotechnology has become an essential tool of many industries. Thus, there is no such entity as "the biotechnology industry." **Biotechnology is a tool employed by several sectors. Each sector faces its own unique advantages and hurdles in the commercialization process. As biotechnology becomes fully integrated, it is often subsumed into the financial markets, regulatory requirements, patent issues, and personnel needs faced by those industries. It is evident, however, that regulatory and patent uncertainty regarding biotechnology may present a temporary slowing of commercialization as new protocols are worked out.**

At present, uncertainties about Federal regulation are being resolved and ambiguities identified. It is likely that biotechnology faces a much different and more stringent regulatory environment than other high-technology sectors. It is too early to assess the impact of regulation on commercial biotechnology, but it can be assumed that regulation will increase the cost of performing R&D and doing business generally.

Current patent battles will set many precedents for future rulings. It is likely, however, that patent litigation in biotechnology will increase given the complex web of partially overlapping patent claims, high-value products, prior publication, and simultaneous production of a product by many companies. And, as patent battles are faced domestically, biotechnology companies will increasingly confront dilemmas of international patent protection. Finally, although trade secrecy is being sought by many companies in addition to patent protection, it is not the desirable route and is considered an unfortunate alternative by many biotechnology patent attorneys.

OTA did not find evidence that the threat of antitrust violations has impeded collaborative efforts in the private sector. One group of industrialists has initiated discussions about the future of private R&D consortia in biotechnology.

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Chapter 7

University-Industry Research Arrangements in Biotechnology

"The interaction of industry with the universities is essential to provide an effective exploitation of the research base. This partnership is critical to our national well-being in an increasingly competitive world marketplace."

White House Science Council
A Renewed Partnership, 1986

"There is justifiable concern that the time may be passing when an individual can produce significant discoveries without outside support and present them as pure gifts to society."

Carnegie Institute
Annual Report of the Staff: The Program in Science Policy 1980-1981, 1982

"To the long familiar military-industrial complex a fraternal twin has been added: an academic-industrial complex through which American and multinational corporations siphon the publicly created resources of our universities and thereby convert publicly financed research into private gain."

Leonard Minsky
"Greed in the Groves: Part II"
The NEA Higher Education Journal, 1984

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Chapter 7

University-Industry Research Arrangements in Biotechnology

INTRODUCTION

The joint funding, performance, and application of scientific work by academic and nonacademic interests is not new (9,11,18,32). Yet in recent years, the rapid proliferation of collaborations in biological research, involving partnerships between universities, industry, and government, has greatly extended the frequency, scope, and visibility of such activities. Attempts to commercialize biological techniques have occurred at an accelerated rate when compared to other fields, involving a much broader spectrum of expertise in its participants, and presenting a greater range of commercial application than discoveries in most other disciplines.

Intellectual capital is the mainstay of biotechnology firms, which, to date, have had little else to market. The importance of the university scientist to commercial biotechnology has been well established. Industrial sponsorship of university research in biotechnology yields substantial benefits to the firms involved. Per dollar invested, industry-supported university research in biotechnology is generating four times as many patent applications as is other company research; 41 percent of the companies investing in university-based research have derived trade secrets from that work (6).

Approximately 46 percent of biotechnology firms support biotechnology research in universities. During 1984, the last year for which data are available, the average Fortune 500 company involved in biotechnology planned to spend $1.1 million on university-directed research, while the average non Fortune 500 company planned to spend $106,000. All totaled, in 1984, biotechnology companies in the United States spent about $120.7 million in grants and contracts to universities. The percentage of industrially sponsored university-based research in biotechnology is approximately 16 to 24 percent; higher than the average 4 to 5 percent spent on overall industry-sponsored campus research (3,6).

Although an increasing number of biotechnology companies are strengthening their in-house research capabilities, available evidence suggests that the private sector will continue to seek the cutting edge provided by the Nation's universities. Direct industry support for all campus research has increased in constant dollar terms every year since 1970. Between 1981 and 1984, this increase was 8.5 percent annually (22). **Even with these increases, industry funding remains small compared to government support of biotechnology research on the Nation's campuses.**

The nature of university-industry biotechnology research arrangements appears to be changing. At an April 1987 OTA workshop on this topic, industry representatives predicted that few companies will invest large sums in universities for long periods for directed research in biotechnology, as was done by Monsanto at Washington University (35). As predicted in the 1984 OTA report on *Commercial Biotechnology*, an increasing number of university-industry arrangements in biotechnology are developing as consulting and contract research rather than long-term research partnerships (36). The predicted time course required to meet industrial expectations of university research requires more pragmatic collaborative arrangements than in the past.

Early concerns about collaborative research arrangements in biotechnology, particularly those involving universities and industry, were focused primarily on issues of academic freedom, proprietary information, patent rights, and other potential conflicts of interest among collaborating partners. As these research arrangements have evolved, and experience has grown, some of the most worrisome difficulties have been resolved, or never realized.

Concerns remain, however, about the subtle impacts of these collaborative arrangements. It is possible that university-industry relationships could adversely affect the academic environment of universities by inhibiting free exchange of scientific information, undermining interdepartmental cooperation, creating conflict among peers, or delaying or completely impeding publication of research results. Furthermore, directed funding could indirectly affect the type of basic research done in universities, decreasing university scientists' interest in basic studies with no potential commercial payoff (3,4,6). In addition, complex and subjective concerns remain about the effectiveness of these arrangements in meeting the needs of participating institutions, and the ability of these new partnerships to stimulate innovation and improve America's competitiveness in biotechnology.

This chapter analyzes the structure, scope, potential problems, benefits, and outcomes of collaborative research arrangements in biotechnology. It focuses primarily on U.S. university-industry research collaborations. (See ch. 4 for collaborations involving State governments; ch. 5 for collaborative arrangements within industry.)

TRENDS IN UNIVERSITY-INDUSTRY RESEARCH IN BIOTECHNOLOGY

During the 1970s, several key factors in the university environment converged to stimulate increasing interest on the part of academic faculty and university administrators in seeking nontraditional funding sources. First, in many fields, research costs were exceeding the available funds from traditional sources—government funding, university budgets, and private foundations (11). Such cost increases have been especially prevalent in fields that require large-scale, technologically advanced equipment and instruments and, consequently, the involvement of larger numbers of technicians with diverse skills (9). Construction grants, as well as direct Federal nondefense R&D support, have fallen annually (37) providing impetus for the university to seek more industrial funds.

Second, increasing Federal budget deficits, soaring inflation, and the change of Administration in 1981 signaled the possibility of some changes in Federal support for university research, which many scientists and university administrators feared would result in drastically cut budgets (11,17).

During this same period, American industry was becoming increasingly aware that its traditional position of "technological supremacy" was being challenged on a variety of fronts, and that its competitive edge in many sectors was in jeopardy (7,28,30). The growing consensus that competitiveness was linked to innovation, and that university research and technology transfer played a critical role in the Nation's ability to compete, led business to show greater interest in creating and strengthening its own connections with the academic community (12).

The putative decline of U.S. industrial competitiveness and productivity soon became a topic of intense public concern, affecting Federal, State, and local politics (11). The assumption that strengthening the links between industry and university research could improve America's economic malaise gave impetus to a variety of new government policy initiatives over the last decade. These included:

- The Patent and Trademark Amendments Act of 1980 (Public Law 96-517), which included changes in Federal patent laws relating to universities. The act changed the presumption of title in inventions made with Federal funds from the government to universities, small businesses, and nonprofit institutions regardless of which agency's funds had been used to make the invention.
- The Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480) to promote cooperative research and technology transfer.

- The 1981 Economic Recovery Tax Act (ERTA) (Public Law 97-34), which provided a 25 percent tax credit for increases in company R&D expenses over and above base-year R&D expense levels and for the contribution of research equipment to universities. Recent revisions of the tax laws have preserved this favorable tax treatment for industrial support of university research, though the benefits are somewhat reduced (8). Under ERTA, limited partnerships formed for the purpose of supporting R&D were also eligible for favorable tax treatment. Many biotechnology companies increased their funding of university research through research and development limited partnerships (RDLPs) (19). (See ch. 5 for further detail.)
- Relaxation of antitrust regulations through the National Cooperative Research Act of 1984 (Public Law 98-462), in part to facilitate research collaborations among previously competitive industrial firms.
- Federal funding for university-industry cooperative programs and projects, for example through the National Science Foundation.
- Growth of State economic development programs that provide incentives to promote university-industry cooperation. (See ch. 4 for further discussion of State programs.)

This confluence of events and policies increased the interest of universities, industry, and government in activities pertaining to partnerships between academia and business in all fields of science. Interest in collaborative research arrangements in biotechnology has been keen because of the potential impact of the resulting products and processes of biotechnology on a diversity of industrial sectors, a multitude of existing and newly proposed Federal and State funding initiatives in this area, and an unprecedented influx of investment capital.

The trend toward academic and business partnerships in biotechnology is expected to continue. However, the growth rate may or may not maintain the pace witnessed in recent years. In part, the rate of future growth will depend on decisions that have yet to be made by industry and on the future availability of trained scientists with significant track records to demonstrate commercial potential.

Some commentators feel that industry will not continue to rely on universities for some of the production-oriented work, and that business is already conducting most of the purely developmental research in house (2,14). Scale-up issues may differ significantly from R&D issues and may be best handled in house. These shifts of resources will obviously change the nature of the collaborative efforts. Concerns about protecting proprietary research may also force industrial firms conducting more development and product-oriented research to work in house in lieu of contracting that portion to the universities. It is likely that new trends in university-industry arrangements will be seen first in the field of pharmaceuticals, with less developed areas of industrial application, such as agriculture, lagging behind. Participants in the April 1987 OTA workshop agreed that industries will continue to rely on universities for cutting-edge research, technical breakthroughs, and support for individual projects, the outcomes of which will result in potential new projects and increased sales (35).

TYPES OF COLLABORATIVE RESEARCH ARRANGEMENTS IN BIOTECHNOLOGY

University-industry research collaborations in biotechnology and in other fields encompass a diversity of approaches. The particular type of interaction that collaborating partners choose depends on their goals and institutional characteristics (27). The relevant factors include:

- *company*: the size, structure, and profitability of the company, the nature of its business, and the progressiveness of its research program;
- *university*: the type, size, and financial health of the university, the relative size and stat-

ure of its science and engineering programs and the orientation of its research and researchers; and
- *externalities*: geographic location, proximity of the collaborating institutions, regional and state economic development initiatives, the location of university alumni in key industrial positions, and the migration of university faculty to industry and vice versa.

Since 1980, many researchers have attempted to develop typologies to categorize the kinds of university-industry interactions that exist. Some of these are generic to all fields (26,27); other categorization schemes are specific to biotechnology (13,18,21,36). However, with so many radically different models all passing under the same general rubric of "research collaboration," it may never be possible to adequately encompass the field in a simple set of categories (31).

One categorization scheme for biotechnology research relationships is shown in table 7-1.

Table 7-1.—Types of University-Industry Research Arrangements in Biotechnology

Between university and firm
- Industry-supported university research: cooperative research programs; jointly run research facilities
- Organized consulting arrangement
- Industrial liaison programs
- Company equity held by university
- University-owned science parks
- Equipment donations by firm
- Company licensed patent owned by university
- Joint commercial ventures
- Consortia

Between faculty members and firm
- Research grants and contracts
- Faculty members as principal officer in firm
- Faculty member on firm's Board of Directors or Science Advisory Board
- Exclusive or non-exclusive consulting with industry
- Full-time summer employment
- Company equity held by faculty member

Between trainees and firm
- Training grants or scholarships
- Direct support of trainee's research
- Trainee salary support, summer or academic year
- Exclusive or non-exclusive consulting
- Informal collaboration

SOURCE: Adapted from D. Blumenthal, M. Gluck, S. Epstein, et al., *University-Industry Relationships in Biotechnology; Implications for Federal Policy*, DHHS Grant #100A-83, submitted to the Office of the Assistant Secretary for Planning and Evaluation, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD, Mar. 20, 1987.

Research Consortia

Biotechnology consortia have been developed by some university-based biotechnology centers to promote technology transfer and raise additional capital. Consortia may include either one company and several universities, several companies and one university, or several companies and several universities. Companies often represent widely differing aspects of the technology in question (e.g., large-scale and small-scale applications). Research tends to be basic with little direct attention to commercialization, but with the implicit or explicit assumption that commercial applications will eventually be available for member companies to pursue independently. Federal or State Government funds often supplement industry funding of these consortia.

Pennsylvania State University, for example, has had 20 sponsoring industries for a cooperative program in recombinant DNA technology and has attracted several industrial sponsors for its Biotechnology Institute. The Center for Biotechnology Research, sponsored by Engenics Corp. (a spinoff of Stanford University) involves six other companies, Stanford University, the University of California, and the Massachusetts Institute of Technology. The University of Wisconsin Biotechnology Center Biopulping Consortium is described in box 7-A. The Midwest Plant Biotechnology Consortium, a group of 15 universities and 30 companies with an interest in plant biotechnology, is described in chapter 10.

Service Facilities

Service facilities are university-based operations that provide, for a fee, the use of equipment, facilities, or expertise to either industry or university scientists. They permit universities to make considerable capital investments in buildings and equipment based on the potential earnings that can be generated through user fees. The Wisconsin Biotechnology Center, the Center for Advanced Research in Biotechnology (CARB) of the Maryland Biotechnology Institute, and the Center for Biotechnology at SUNY Stonybrook are examples of service facilities.

Box 7-A.—The University of Wisconsin Biopulping Consortium

In April 1987, the University of Wisconsin's Biotechnology Center and the U.S. Department of Agriculture's Forest Products Laboratory joined to develop a biopulping research consortium. Boise Cascade Corp., Celulosa Puerto Piray SA of Argentina, Consolidated Paper, Inc., Dow Chemical Co., Great Northern Nekoosa Corp., James River Corp., Mead Corp., Potlatch Corp., Procter & Gamble Co., Sandoz Chemicals Corp., Scott Paper Co., Spout-Bauer, Inc., and Weyerhaeuser Co. each contributed $15,000 annually during an initial 5-year period to support the project. The Biotechnology Center will join the 13 founding companies as the fourteenth contributor to the project.

The biopulping process has the potential to improve on present mechanical and chemical methods by reducing energy, capital costs, and environmental treatment requirements. The process would use enzymes from a naturally occurring white rot fungus known as *Phanerochaete chrysosporium* to separate lignin from cellulose in a selective manner. When dilignification with fungi is combined with mechanical pulping, energy consumption drops by 25 percent. The consortium's initial research is focusing on whether this process can adapt to large-scale pulp production.

Corporate sponsors will have access to the research on an ongoing basis through an information service, a yearly symposium, and direct interaction with staff members. Industry sponsors are expected to play an important role in both identifying needs and transferring the technology to onsite applications.

SOURCES: *Pulp and Paper Week*, Apr. 6, 1987; and J. Kelley, University of Wisconsin Biotechnology Center, personal communication, 1987.

Photo credit: University of Wisconsin-Madison

The Protein/DNA Sequence/Synthesis Facility at the Biotechnology Center of the University of Wisconsin-Madison.

- In Wisconsin, the Biotechnology Center operates a number of pay-back facilities. If a startup firm needs a monoclonal antibody, it can be made at the Center for a fee, avoiding for the firm the cost of investing in equipment necessary for monoclonal production. The Hybridoma Facility offers three options to clients desiring hybridoma production, screening, cloning, or antibody production—full service, self service (inexperienced), and self service (experienced). Another facility offers services in protein purification and obtains equipment through shared equipment grants. A Plant Cell and Tissue Culture Facility offers instruction, protoplast isolation and plating, media preparation, anther culture, and long-term storage of plants in test tubes. Additional facilities include the Transgenic Mouse Facility, the Protein/DNA Sequencing/Synthesis Facility, and the Biocomputing Facility.
- At CARB, advanced computer graphics capabilities and x-ray crystallography equipment will be available for companies willing to pay for structure analysis in protein engineering and rational drug design.
- At the Center for Biotechnology at the State University of New York at Stonybrook, service facilities are provided by the Hybridoma Center, the Center for the Analysis and Synthesis of Macromolecules, and the Center for Radioligand Synthesis and Spectroscopy.

POTENTIAL BENEFITS OF UNIVERSITY-INDUSTRY COLLABORATION IN BIOTECHNOLOGY

Historically, the potential for new economic and social benefits from scientific research has helped scientists secure funding and, at times, social stature for their work (9). More recently, scientific research—especially collaborative research between industry and universities—has been targeted as one of the critical elements in stimulating technological innovation, enhancing industrial competitiveness, and in achieving sustained economic growth and development, both regionally and nationally. In fact, nearly every statement on America's current economic predicament cites the university as the source of new scientific and technological breakthroughs, and university-industry partnerships as the vehicle through which sustained economic recovery will be achieved (18).

Whether university-industry collaborations can make good on these claims has yet to be determined. To date, there have been no rigorous, empirically based, national studies of the outcomes of these collaborative arrangements. Part of the problem is that many of these collaborations are too new to assess. OTA recently sponsored one of the few studies of the outcomes of collaborative research arrangements in advanced materials, information technology, and biotechnology (31). The findings of that study suggest that commercial outcomes—products and processes—have been fairly limited to date, and that outcomes are heavily contingent on how the collaboration is structured and managed.

One survey of industrial firms with university-industry research relationships in biotechnology asked respondents for their list of perceived benefits of collaboration (3,4). Factors perceived by 50 percent or more of these industrial respondents as benefits "to a great or some extent" (in order of priority) were:

- the likelihood of the collaboration resulting in product or process licenses;
- the ability of the company to keep current with important research;
- reduction in costs of mounting R&D programs in a new field;
- enhancement of the firm's public image; and
- training and staff development for company scientists.

From the university perspective, some benefits cited in another study include:

- improvement in the level of research and training in applied science;
- transfer of technology to industry and greater relevance to society; and
- assistance in offsetting uncertainties of Federal R&D support (13).

Except for expectations of the profound commercial potential for biotechnology-related products in a variety of sectors (e.g., agriculture, chemicals, pharmaceuticals), many of the benefits cited are similar to ones described as motivators in other fields of science.

Benefits for the Universities

Money, in a variety of guises, could be a primary benefit to the university of industrial sponsorship of research: money for research, the opportunity for equity participation, limited investment in physical plant and facilities, and the associated added income for faculty. Further, inflation in the late 1970s and the fear that current support for basic research would be cut forced many universities to tap several sources for funding and equipment. Ninety percent of the universities responding to a recent survey report receiving some industrial funds to conduct research in biotechnology (3,4).

Evidence suggests, however, that large capital infusions, such as those which occurred between Hoechst and Massachusetts General Hospital, may be the exception rather than the rule. In 1984, 60 percent of industrially funded biotechnology projects at universities were funded at less than $50,000, 20 percent were funded for $50-100,000, and only 20 percent were funded for over $100,000 (6).

Furthermore, it is not clear that the financial benefits to universities, other than direct support itself, have been realized. Eighty nine percent of the sampled universities realized at least one patent from biotechnology research over the past 5 years, but substantial income from licenses is rare, and earnings fail to exceed the cost of administering the patents and licenses. In addition, few universities own equity in any biotechnology company owned or founded by their faculty, and even fewer reported any substantial appreciation in such holdings (6). **It seems unlikely, therefore, that university-industry relationships in biotechnology have or will significantly meet the unmet capital needs of universities.**

The real benefit from university-industry research collaborations could be the capacity to do things neither partner could do alone. Industry may provide critical leverage to university applications to Federal and private funding agencies. For many university scientists, industrial sponsorship provides the added excitement and prestige that comes from working on truly cutting-edge scientific research and entering into long-term agreements with industry (2,24). Collaborations with industry may also help the university retain faculty members who might otherwise leave, and to attract new faculty and students. Industry collaborations may allow smaller, less prestigious universities to build their research base and to offer training opportunities for students. Since many of the small, less well known universities often have trouble gaining access to research funds at the National Institutes of Health and elsewhere, the use of industrial capital to build their research capability would offer great benefit.

Benefits for Faculty

In a survey of over 1,200 faculty members conducted at 40 major U.S. universities, approximately 47 percent of biotechnology faculty reported consulting with an outside company, and 8 percent reported holding equity in a firm whose products or services are directly related to their own university research. The survey also revealed that biotechnology researchers with industrial support publish at higher rates, patent more frequently, participate in more administrative and professional activities, and earn more than colleagues without such support (6).

Table 7-2 summarizes the responses of biotechnology faculty, with and without industry support, to questions of the perceived benefits of university-industry collaborations (6). The table shows that the majority agreed that such arrangements involved less red tape than does Federal funding and increased the rate of practical applications from basic research. The table also illustrates some interesting differences between biotechnology faculty with industrial support and those not receiving funding from this source.

Benefits for Students

Although the literature on the effects of university-industry collaborations in biotechnology is replete with anecdotes about the problems such relationships can cause for graduate and postdoctoral training, one study found that students do not feel that their training is being shortchanged or that the quality of their educational experience is being compromised (10). In fact, the students surveyed generally felt that "the benefits outweighed the risks." There is no evidence to date suggesting that students working in labs with industrial support are getting less guidance or receiving insufficient faculty attention. Compared to colleagues without industrial support, biotechnology faculty with industrial support seem to spend comparable amounts of time each week with graduate students and postdoctoral fellows (3,4).

Industrial sponsorship can provide increased fellowship opportunities and more employment opportunities for students when they graduate. Not everyone taught can or wishes to go into academic science. The results of a 1985 survey of personnel needs in biotechnology firms conducted by the Institute of Medicine and the American Society for Microbiology revealed that there has been a substantial increase in the number of scientists employed in the biotechnology industry since 1983 (16). (See ch. 8 for further discussion of personnel and training.)

In addition, exposure to industrial projects can provide students with the opportunity to conduct more research, gain knowledge of industrial applications, and learn how to test hypotheses. Students funded by private firms may be more likely than those without industry connections to report patents resulting from their research (3). Those students are often offered permanent po-

Table 7-2.—Benefits of University-Industry Collaborations Reported by Biotechnology Faculty

Question	"To some extent or to great extent" (%) Industry support	"To some extent or to great extent" (%) No industry support
To what extent does industry research support:		
• Involve less red tape then federal funding	76	51[a]
• Increase the rate of applications from basic research	67	52[a]
• Provide resources not obtainable elsewhere	63	36[a]
• Enhance career opportunities for students	60	43[a]
• Enhance scholarly productivity	41	20[a]
• Produce patents that increase university revenues	41	33

[a] Significantly different from faculty with industry support ($P<0.01$).

SOURCE: D. Blumenthal, M. Gluck, K.S. Louis, et al. "University-Industry Research Relations in Biotechnology: Implications for the University," *Science* 232:1361-1366, June 13, 1986.

sitions because of their familiarity and experience with industrial research problems (1).

Benefits for Industry

A 1984 survey of biotechnology companies revealed that the investments these companies were making in university research seemed to be yielding substantial benefits to the firms involved (3,4). Per dollar invested, university research generated more patent applications than company research. Whether these patent applications will result in marketable products or processes and profits for the sponsoring firms has yet to be determined. Collaborative research with universities constitutes a relatively small part of most firms' R&D investment, generally less than 10 percent. For an important minority, such collaborations constitute a significant part of their research (6).

Clearly the commercial potential in biotechnology-related processes and products is one of the primary benefits that industry perceives it will gain through university-industry research collaborations, but it is not the only one that industry values. Industry has to master this technology to do its own research. Collaborations with universities permit industry to buy in at a relatively low cost, without having to recreate the resources and talent already available in academia. Academic-business research relationships allow businesses to tap otherwise inaccessible brainpower, increasing their competitive edge. Thus, collaborations enable industry as well as universities to accomplish tasks neither could tackle alone.

POTENTIAL PROBLEMS OF UNIVERSITY-INDUSTRY COLLABORATION IN BIOTECHNOLOGY

Concerns about the commercialization of academic biomedical research probably reached a zenith around 1981, about the same time that the House Committee on Science and Technology convened its first hearing on the subject (33). The hearings focused on two major issues: whether university-industry research relationships violated scientific and academic freedom and responsibilities, and whether these relationships best served the interests of the American public.

By the time the Committee convened its second set of hearings, nearly one year later, some of the initial controversy had subsided (34). Then Congressman Gore said in his opening remarks: "We do not view such agreements as bad per se, but rather as a development that needs to be examined in detail." However, this kind of detailed examination has not taken place. With the exception of a few isolated studies, little evidence exists to either substantiate or refute the largely rhetorical claims of those who feel great harm is being done to academic science as a result of the new "university-industrial complex."

In one study of university-industry research interactions, the scientists and administrators surveyed raised a variety of concerns (26). Most of the issues were not mentioned more than 25 percent of the time by either company or university representatives, although academic respondents clearly raised more concerns about the research interactions than their industrial counterparts. Both parties expressed concern about basic vs. applied research. About 23 percent of university representatives raised concerns about academic freedom. None of the other issues—adverse impacts on research quality, credibility, continuity, and the commingling of funds—appeared to be of major concern to either industry or university respondents.

In general, the perception of potential problems that can result from university-industry collaborations in biotechnology does not differ from that seen in other fields. However, the degree and frequency with which problems are occurring is perceived to be intensified in biotechnology, perhaps because of the accelerated proliferation of these partnerships in a relatively short time.

Problems for Universities

Comments from analysts of university-industry collaboration about the problems universities are experiencing in collaborative arrangements range from "the problems are many" to "the problems have been beat to death." At issue is whether and to what degree universities should remain detached from the world of business. (Some question whether this idealized (or idolized) kind of academic environment ever existed at all.) Yet regardless of viewpoints, observers interviewed by OTA seemed to agree that universities are indeed being changed by their research relationships with industry.

One frequently cited problem concerns secrecy. Some analysts maintain that colleagues cannot exchange information, despite its intellectual potential, because of its commercial value. Others argue that a delay in publication of six months makes little difference and that trade secrets tend to be on the production side, not the basic research side. Some contend that as corporations bring development-oriented activities in house, the secrecy issue will diminish on the campus. But in one study, 25 percent of industrially supported biotechnology faculty reported that they have conducted research that belongs to the sponsor and cannot be published without prior consent; and 40 percent of faculty with industrial support reported that their collaboration resulted in unreasonable delays in publishing (3). When research approaches the point of publication, the company may request that certain pieces of information be withdrawn because they may reveal a trade secret, such as the composition of a buffer, or formulation of a pharmaceutical compound.

Several commentators interviewed by OTA expressed concern about interdepartment and intradepartment competition for scarce resources and the potential imbalances in resource allocation that university-industry collaborations can cause. The possibility was raised that this competition would cause some fields within the university to atrophy. For example, a $32 million Biological Sciences Complex at the University of Georgia apparently has drawn funds, and criticism, from other instructional programs.

Problems for Faculty

The potential problems for universities and faculty members engaged in collaborative arrangements include:

- impacts on the university's research agenda, such as the potential for professors to orient their research toward products that could have commercial value or the shifting of research to accommodate corporate sponsors;
- conflicts of interest, such as the use of university equipment for private gain or the shift of time away from university responsibilities;
- exploitation of students as inexpensive labor or outright neglect of students by faculty who become increasingly involved in commercial projects; and
- interruptions in the free flow of information and materials among colleagues because of patent-induced publication delays, trade secrets, and other proprietary inhibitions—the "publish or profit" problem (18). Faculty with industry funds are much more likely than other biotechnology faculty to report that their research has resulted in trade secrets and that commercial considerations have influenced their choice of research projects (3).

Table 7-3.—Risks Reported by Biotechnology Faculty

	"To some extent or to great extent" (%)	
Question	Industry support	No industry support
To what extent does industry research support pose the risk of:		
• Shifting too much emphasis to applied research	70	78[a]
• Creating pressures for faculty to spend too much time on commercial activities	68	82[b]
• Undermining intellectual exchange and cooperating activities within departments	44	68[b]
• Creating conflict between faculty who support and oppose such activities	43	61[b]
• Creating unreasonable delays in the publication of new findings	40	53[b]
• Reducing the supply of talented university teachers	40	51[a]
• Altering standards for promotion or tenure	27	41[b]

[a] Significantly different from faculty with industry support ($P<0.05$).
[b] Significantly different from faculty with industry support ($P<0.01$).

SOURCE: D. Blumenthal, M. Gluck, K.S. Louis, et al., "University-Industry Research Relations in Biotechnology: Implications for the University," *Science* 232:1361-1366, June 13, 1986.

None of these problems, however, is unique to university-industry collaborations. The quest for grants, prizes, and status has often led to secrecy before research results are published.

In addition, university-industry collaborations could cause imbalances of faculty, students, and space, shake public confidence, and jeopardize government funding (25). Furthermore, collaborations could threaten the scientist's objectivity, although there is no hard evidence that academics with industrial ties are in fact less objective in their judgments, or less interested in scientific truth (20,21,29). Table 7-3 presents the risks reported by biotechnology faculty with and without industrial support.

The most frequently cited problems for faculty involved in collaborative research relationships with industry are the potential conflicts inherent in having mixed allegiances. The danger is that faculty will spend a disproportionate amount of time on applied research and commercial interests. Industry supports research that is more likely to be applied.

Faculty members with industry support are more than four times as likely as faculty without industry support to report that their choice of research topics has been influenced by the likelihood that the results would have commercial application (6). Although companies may selectively support faculty whose research has commercial potential, biotechnology faculty with or without industry support seem to feel that industrial support does shift research in applied directions.

Critics of the university's involvement in industrially oriented research are concerned that the more one engages in outside commercial activities, the less one devotes to university responsibilities. However, one study seems to suggest the opposite (3,4). Biotechnology faculty with industrial support exhibit enhanced productivity in several areas, including university activities, and show no significant declines in teaching time. Teaching time may not be an appropriate measure of the effects of commercial activities, since the content and quality of that teaching, and the material contained in the coursework itself, may be more relevant.

Problems for Students

In a recent survey of students, over 25 percent either received direct support from industry for their research (12 percent) or worked in labs of investigators who received industrial funds (an additional 15 percent) (6). There is a great deal of discussion, but little reported in the literature, about the effects of university-industry relationships on students and postdoctoral fellows. The fear that students could be exploited by commercial priorities or the pecuniary interests of their professors, and that their education and training may be compromised, was often expressed in OTA interviews with academic scientists.

One study (10) adds some empirical data to an area in which the only evidence of problems for students to date has been in the form of newspaper articles and anecdotes. The study surveyed

693 graduate students and postdoctoral fellows at six research-intensive U.S. universities, assessing the effects of industry-sponsored university research in the life sciences, and more specifically in biotechnology. The study revealed that students with industrial support published about a third fewer papers, reported more significant delays in publication, and reported inhibitions in discussing their work with colleagues more frequently than their peers. Some students and fellows with industrial support must work on projects chosen by industry, or provide other services to their industrial sponsors. Industry-sponsored research tends to be more applied, which may, in part, explain the lower rate of publication.

Problems for Industry

Industry would appear to face few problems from university-industry research collaborations. Obviously, if an agreement is not viewed as successful, a company can elect to discontinue support. The major concern of industry could be whether these academic-business partnerships in biotechnology will result in the revolutionary new products and processes currently envisioned.

Exclusivity is an expectation of firms sponsoring collaborative research. The scientist's or university's ability (or willingness) to grant exclusivity may be a point of contention. Furthermore, since many parties could be involved in the collaboration, the designation of rights may become more complex. **As projects come to fruition in multi-party collaborations, who negotiates the contract with industry, who holds the contract, and how property rights are assigned will be major issues facing industry, as well as all parties involved.**

One particularly problematic scenario involves a consortium involving Federal, university, and industrial funds. As a result of the collaboration, a company could gain title to patents based wholly or partly on Federally funded work. Existing law requires that patents resulting from Federally funded research in universities be owned by the university or the Federal Government (if the university has an institutional patent agreement with the granting agency)(15). Thus, if the university permits patent title to the company, it could be in violation of the law. Self-interest on the part of the university may be the best protection against such a violation given the logical desire for the university to retain patent ownership.

Findings from a 1986 industrial survey (3,4) suggest that companies sponsoring university research also perceive potential risks in university-industry relationships. Problems perceived by over 20 percent of the firms as a potential risk "to a great or some extent" were:

- poor payoff in marketable products (62 percent);
- loss of proprietary information (58 percent);
- excessive monitoring and controlling effort (42 percent); and
- university withdrawal from the relationship before the firm receives anticipated benefits (21 percent).

VARIABILITY IN THE BENEFITS AND PROBLEMS

Many of the researchers and commentators who discuss the benefits and the problems of university-industry research collaborations in biotechnology often speak as if academia and business were monolithic entities. Obviously, this is not the case. Universities vary enormously in their structures, values, objectives, orientations, and responses toward collaborative research. The diversity of U.S. industrial firms on these dimensions is probably even greater. Consequently, the type of university-industry research arrangement that works for an Eastern Ivy League university may be very different from one that fits a land grant college in the South or the Midwest; the motivations and expected outcomes of a large multinational corporation that collaborates with a university—such as Monsanto's agreement with Washington University—undoubtedly would vary greatly from those of a start-up venture like Embryogen and its relationships with Ohio University. Because these differences may affect the benefits and problems experienced by collaborating partners, analysts must go beyond the generalities and document some of these variations.

In a recent OTA study of collaborative research arrangements (31), the particular type of organizational structure was not highly correlated with benefits or outcome measures; the same could be said for problems. What is more likely—although additional research is needed in this area—is that the potential problems for the university and its faculty may be tied to the degree to which a particular arrangement interferes with faculty duties and the level—individual or institutional—at which the agreement is made. From an industrial point of view, benefits are in part tied to these two factors as well, but the direction of the causation is probably reversed.

Variability Among Industrial Partners

It is not possible to explore all the differences among industrial partners that can affect university-industry research collaborations in biotechnology. Furthermore, there are times when the same company enters into different types of agreements with separate universities, each characterized by its own pattern of interactions and outcomes. An example is Monsanto's agreements with Harvard and Washington Universities. One variable may be distinctive in the relationships between universities and businesses—the size of the collaborating partner.

Discussions with industrialists, both large and small, suggest that collaborations with small firms seem to constitute the greatest gamble for universities. Compared to larger firms, small firms are more likely to support faculty with significant equity in their companies, report the use of trade secrets, and fund projects of very short duration.

On the other hand, the financial benefits of relationships with small firms may be considerable. These arrangements seem to produce many more patent applications per dollar invested than do relationships with large firms (3,4). However, the applications for patents held by universities may not produce profitable licenses, and relationships with large companies seem smoother and less complicated with fewer conflicts of interest.

The benefits to individual scientists may be greater with large companies, which are more likely to supply a steady stream of money over the long term (20). However, not all the experts interviewed by OTA perceived small firm collaborations as potentially risky. Much depends on the type of university involved and the way that institution perceives its missions vis-à-vis industry (23). There may be potential risks in collaborating with companies large enough to buy an academic department (14).

Variability Among Sectors or Areas of Research

Little is known about sectoral variations in the nature of university-industry collaborations in biotechnology (e.g., agriculture, chemicals, pharmaceuticals). The major sectoral differences involve orientation and focus: product vs. process. Since companies are most interested in products which can yield the greatest potential gain, the most frequent and intense university-industry research collaborations seem to be taking place in pharmaceuticals. In agriculture, while there are proprietary plants, the research problems are thought to be more complex and the envisioned products more long term. Hence, the degree of collaboration has not been as intense. This is likely to change. In chemicals, where the research is more applied, a large proportion of the research can be done in corporate labs or through consulting, decreasing this sector's dependence on university-industry research relationships.

Some argue that biotechnology firms have already altered the nature of problem selection by academic scientists; problems dependent on the elaboration of technique, not theory, are emphasized. Consequently, in university-industry research relationships, corporations are focusing on the development of biologicals (e.g., enzymes, pharmaceuticals) because of the likelihood of more rapid commercial payoff. Thus, problems requiring that substantial theoretical obstacles be crossed before technical breakthroughs can be achieved (e.g., the control and transfer of nitrogen fixation in the agricultural sector) are receiving less immediate attention in collaborative research partnerships.

Variability Among Universities in Their Responses to Collaborative Research Arrangements

Just as collaborative arrangements vary tremendously depending on their form, structure, and research area, universities exhibit a great deal of diversity in their responses to the benefits and problems that can result from university-industry research relationships. Differences in response include:

- the amount of time allowed to faculty for outside consulting, or for the management of or involvement in entrepreneurial activities;
- the degree to which faculty can use university equipment, facilities, and staff (including students) in nonacademic, commercial research;
- sanctions against, or incentives for, universities to become financially involved in the start-up or spinoff ventures of faculty (e.g., equity interests in ventures seeded, funding incubator centers);
- whether the university, industrial sponsor, or individual scientists retain intellectual property rights or the exclusivity of such patents, licenses, and trade secrets;
- the amount of time deemed acceptable to delay publications prior to or simultaneous with patent filings; and
- whether university scientists or industrial sponsors (or some combination of the two) set research priorities and the research agenda.

There are few standards in place throughout the academic community on the six dimensions just described. Rather, each institution is meeting the challenge of setting its own boundaries of acceptability in ways that are consistent with its characteristic culture and mission. Some analysts believe that the largest, most prestigious universities must be the ones to stand up to the potential risks of industry-university collaboration and set the standards for other institutions to follow (23).

Too simplistic are assumptions that a continuum can be constructed to characterize the nature of collaborative research arrangements in biotechnology and that problems would intensify as the ties between academia and business intensify. Problems and benefits exist at all ends of the continuum. Furthermore, rather than a linear continuum, there exist multiple axes at any moment in time (e.g., type of arrangement; size of industrial partner; university culture; area of research).

SUMMARY AND CONCLUSIONS

In the long run, the trade-offs made between the potential benefits that accrue from university-industry research collaborations in biotechnology and the potential problems and risks associated with such relationships will depend on how the public and the policy-making community value the outcomes of these new partnerships. Two issues that must be balanced are:

- whether losses to science or to university values that result from increases in the level of secrecy in universities are offset by net additions to knowledge that result from the infusion of industry funds into university laboratories; and
- whether shifts in the direction of the university research agenda toward more applied and commercially relevant projects have benefits for human health and economic growth that far outweigh the risks to basic research.

University researchers are not the only ones concerned with the trade-offs. Others have said that it is truly in the national interest to develop new institutional arrangements that are potentially capable of reducing the time lag between advances made in the basic research laboratory and the application of those advances to human service (33). Advocates of active university-industry collaboration assert that the public interest is best served when the results of research are published and made available to the scientific community, and the academic work that is commercially valuable is patented and does in fact reach the marketplace faster through collaborations between the universities and the industrial community.

In the meantime, there are measures that can be taken to strengthen university-industry research relationships for all participants, and to maximize some of their potential benefits, while minimizing their problems and risks. Universities and the industrial firms involved could ease the introduction of academic-business partnerships on campus with extensive prior discussion in which all relevant parties including students, faculty, university administrators, and corporate executives participate.

Universities can negotiate collaborative agreements that are consistent with the values and missions of their institutions and can include as essential elements of any such agreement:

- the scope of the agreement (e.g., particular research area(s) supported; time commitments of faculty participants);
- control over the conduct of the research (e.g., who selects areas of research, specific projects, and methodologies; provisions for internal and/or external advice and review);
- sponsor's responsibilities (e.g., funding; staff support; equipment; materials contributed);
- treatment of proprietary information;
- publication requirements (e.g., pre-publication review delays); and
- patent rights and income (e.g., title retention; license agreements; term or life of the patent).

Once established, universities can monitor their collaborative research relationships with industry and rigorously enforce:

- disclosure rules;
- conflict of interest statutes;
- limitations on excessive outside consulting by faculty members; and
- sanctions against faculty that retain "full-time" status at the university and are simultaneously executives in their own companies with "full-time" management responsibilities.

It has been suggested that Federal law or regulation should dictate what is considered in and out of bounds for universities in their interactions with industry. A violation of the rules would mean a cut off of Federal funding for the university in question (18). While such an approach is extreme, **the issue of private gain from public investment requires some degree of accountability.**

Those who take a negative view of university-industry research relationships may be arguing for a return to a perceived simpler time, when academics were academics, and businessmen were businessmen. Times have clearly changed, and both the internal and external demands on the university are increasing and sometimes conflicting. Perhaps the most obvious example of those changes and conflicts is the ever-closing gap between business and academia in U.S. biotechnology.

Even though industrial support for university research in biotechnology has clearly changed the dynamics of that field at the individual and institutional levels, **any funding source has the potential of influencing the research agenda and those that conduct the sponsored research.**

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Chapter 8

Training and Personnel Needs in Biotechnology

"Most of our technology walks out every night in tennis shoes."

Robert Swanson
Genentech

"The key to educating a biotechnologist is flexibility in specialized aspects of a program that is firmly based in science and engineering."

David Pramer
Rutgers University

"The biotechnology revolution . . . has changed in *fundamental* ways how biologists and chemists regard their disciplines and therefore how those disciplines may properly be taught."

Budget Change Proposal
California State University
Center for Biotechnology Education and Research

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Chapter 8

Training and Personnel Needs in Biotechnology

INTRODUCTION

The continued commercialization of biotechnology in the United States depends on trained scientific and technical personnel. High-technology firms consistently rank quality of education and the availability of a skilled work force among the most crucial elements for success (16,30), and access to educational facilities is often pivotal in decisions about where to locate biotechnology firms (30).

Biotechnology is not one discipline but the interaction of several disciplines to apply scientific and engineering principles to the processing of materials by biological agents to provide goods and services (37). Thus, currently practicing "biotechnologists" were not trained as such, but were trained in such fields as molecular biology, genetics, biochemistry, microbiology, botany, plant pathology, virology, biochemical engineering, fermentation technology, and others. Much of the training for biotechnology continues to be in these and related areas.

Biotechnology personnel needs will change as the industry continues to grow and mature. The shift in emphasis from research and development (R&D) to production, for example, requires more bioprocess engineers and more technicians. Applications in new industrial sectors will also change personnel requirements. While the pharmaceutical industry is currently the predominant user of biotechnology, agriculture is also a significant user and other industrial sectors are increasingly applying biotechnology. Future personnel needs in biotechnology will depend on the R&D needs, the products that are produced, and the extent to which biotechnology is integrated into various industries. While most industry analysts and academics agree that the number of biotechnology personnel needed will continue to grow in the next 5 to 10 years, opinions vary on the specific types of jobs that will be available and the type of training required for these jobs. U.S. colleges and universities have responded to the perceived personnel needs in biotechnology with a variety of new training and educational programs.

SIZE AND FUTURE GROWTH OF COMMERCIAL BIOTECHNOLOGY

Few analysts expect biotechnology to generate a large number of new jobs, but its applications are growing rapidly and its personnel needs are often for specific, highly trained individuals. **OTA estimates the total personnel working in biotechnology for dedicated biotechnology companies (DBCs) and large, diversified companies to be about 35,900, of whom 18,600 are scientists and engineers.** While this indicates at least a five-fold increase in employment since 1983, the total numbers are low when compared with other high-technology sectors. Computer and data processing services, for example, employed almost 600,000 workers in 1986 (58).

A range of figures has been published on biotechnology employment in the past 5 years (table 8-1). A 1982 report estimated the total U.S. private sector employment in "synthetic genetics" to be 3,278, with an annual growth rate of 54 percent (26). Using data from a 1983 OTA/National Academy of Sciences survey, OTA estimated employment in U.S. biotechnology R&D work force to be 5,000 (72). Using data from a similar survey conducted in 1985, the Institute of Medicine (IOM) estimated that 12,000 scientists were employed in the biotechnology industry that year (39). A 1986 report estimates that 15,959 scientists and technicians are working in biotechnology (62). The

Table 8-1.—Estimates of Employment in Biotechnology, 1982-87

Year	Source of Estimate	Estimated Number Employed	Employment Sectors
1982	Feldman & O'Malley[a]	3,278 (total employees)	Private sector
1983	Office of Technology Assessment[b]	5,000 (R&D employees)	Biotechnology companies (based on total of 219)
1985	Institute of Medicine[c]	12,000 (scientists only)	Biotechnology companies (based on total of 282)
1985	National Science Foundation[d]	7,000 (scientists and engineers)	Biotechnology companies and large corporations[e]
1986	Center for Occupational Research and Development[f]	15,959 (scientists and technicians)	Biotechnology companies, (based on total of 242)
1986	National Science Foundation[d]	8,000 (scientists and engineers)	Biotechnology companies and large corporations
1987	U.S. Department of Commerce[g]	25,000 (overall employment)	Dedicated biotechnology companies (based on a total of 300)
1987	Office of Technology Assessment[h]	13,221 (scientists and technicians) 24,347 (overall employment)	Dedicated biotechnology companies (based on total of 296)
1987	Office of Technology Assessment[i]	5,360 (scientists and technicians)[i] 11,600 (overall employment)	Diversified companies (based on total of 53)
1987	Office of Technology Assessment	18,581 (scientists and technicians) 35,947 (total biotech employees)	Diversified and dedicated biotechnology companies

[a] M. Feldman and E.P. O'Malley, *The Biotechnology Industry in California*, contract paper prepared for the California Commission on Industrial Innovation, Sacramento, CA, August 1982.

[b] U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Analysis*, OTA-BA-218 (Elmsford, NY: Pergamon Press, Inc., January 1984).

[c] Institute of Medicine, Committee on National Needs for Biomedical and Behavioral Research Personnel, National Academy of Sciences, *Personnel Needs and Training for Biomedical and Behavioral Research (1985 Report)* (Washington, DC: National Academy Press, 1985).

[d] National Science Foundation, *Biotechnology Research and Development Activities in Industry*, Surveys of Science Resources a Series, Special Report, (NSF 88-311) (Washington, DC: 1987).

[e] Ninety-four firms were estimated to represent two-thirds of the industry's activity.

[f] B.F. Rinard, *Education for Biotechnology* (Waco, TX: The Center of Occupational Research and Development, 1986).

[g] U.S. Department of Commerce, International Trade Administration, *1988 U.S. Industrial Outlook* (Washington, DC: Government Printing Office, January 1988).

[h] U.S. Congress, Office of Technology Assessment, Survey of Dedicated Biotechnology Companies, 1987.

[i] U.S. Congress, Office of Technology Assessment, Survey of Diversified Corporations in Biotechnology, 1987.

National Science Foundation (NSF), however, estimated that only 8,000 scientists and engineers worked primarily in biotechnology as of January of 1986 (56). A reason for the difference is that NSF has assumed fewer companies are performing the bulk of biotechnology R&D than the other estimates, and NSF considered only personnel involved in R&D, not production (18,56). The U.S. Department of Commerce recently estimated that 25,000 people worked for dedicated biotechnology companies (76). This estimate is very close to OTA's estimate, derived from a survey of dedicated biotechnology.

Current Survey Results

In the spring of 1987, OTA surveyed dedicated biotechnology companies (DBCs). Firms were divided into small (1 to 20 employees), medium (21 to 100 employees), and large (101 to 1,000 employees). The numbers of small and medium firms were nearly even at 112 and 121, respectively. Only 56 companies employ 101 to 1,000 people. (See ch. 5.) The average company had 86 employees, and the median response was 30. Private companies averaged 40 employees, while public and subsidiary companies were approximately equal in size with an average of approximately 165 employees. Companies working in human therapeutics, plant agriculture, and human diagnostics tended to be the largest in the industry, averaging 120 employees. Specialty chemicals and reagents companies tended to be smaller, with 30 to 45 employees. Chapter 5 discusses other sectoral differences of commercial biotechnology.

The OTA survey of DBCs found that 135 companies employed a total 11,597 people, of whom 6,297 or 54 percent were scientific and technical personnel. Extrapolating these figures to the total of 296 biotechnology firms identified for the survey gives a total employment figure of 24,347, of which 13,221 would be scientific and technical personnel.[1] A second OTA survey covered 53 diversified corporations involved in biotechnology research and development. The survey showed these 53 companies, including large chemical, pharmaceutical, and agricultural companies (see ch. 5), employed 11,600 in biotechnology, of whom 5,360 were scientists and engineers with advanced degrees. OTA estimates that the current number of scientists and engineers employed in biotechnology is at least 15,000 to 21,000, with an additional 15,000 to 19,000 nontechnical personnel working for biotechnology companies. These ranges are probably slightly lower than the actual total, as not all large corporations involved in biotechnology could be identified and surveyed, and more dedicated biotechnology companies have been identified since the 296 were surveyed (see ch. 5 and apps. A and B).

The future rate of growth of employment in biotechnology will depend on the success of companies in introducing products and services based on biotechnology, the expansion of biotechnology applications in new fields such as waste management and the extraction industries, and investor confidence in biotechnology. Companies contacted for a survey for the Industrial Biotechnology Association (IBA) expected their staffs to grow an average of 44 percent from July 1, 1987 to June 30, 1989 (38). If companies grew at their hoped for rates, the biotechnology work force would number almost 58,000 by June 1989 (70). Companies responding to the OTA survey also reported high levels of employment growth, averaging 27.4 percent over the next 5 years. In 1983, companies expected to increase their staffs by 42 percent during the next 18 months. They actually increased their staffs by 20 percent (39). While companies can be expected to be optimistic, growth in biotechnology employment is indicated. According to analysts with the Bureau of Labor Statistics, the overall number of life scientists is expected to grow 21 percent or 30,000 jobs between 1986 and the year 2000, largely because of increasing applications of genetics research (67).

Personnel Needs in Biotechnology

Personnel needs in biotechnology are changing with the maturation of the industry. Each stage of development requires different activities and skills. Early stages mainly require research scientists and supporting laboratory technicians. As potential commercial products are developed, bioprocess scale-up engineers, cell culture and fermentation specialists, separation and purification specialists, analytical chemists, clinical scientists, regulatory affairs experts, and financial analysts are required. When full-scale production is underway, technicians at a variety of levels and quality control specialists are needed, as well as marketing managers and other business specialists.

This changing mix of personnel at biotechnology companies is becoming evident. Production and quality control positions are being added to the R&D jobs that have been the mainstay of employment. The current trend is toward hiring technicians rather than Ph.D. level researchers (47). Opportunities for biologists and biochemists at the master's and bachelor's level (38) and perhaps even with 2-year associate of applied science degrees (62) will increase. Currently, according to data from OTA's survey of DBCs, Ph.D. scientists represent 14 percent of company personnel and 28 percent of scientific personnel. This demonstrates a continuing decline in Ph.D.s as a percentage of the scientific work force in biotechnology. Data from OTA's 1983 survey showed that 43 percent of R&D personnel held Ph.D.s., while the Institute of Medicine reports that 38 percent of the scientists employed in biotechnology firms held Ph.D.s in 1985 (39).

Biotechnology firms are also shifting somewhat from researchers to managers and marketers (17). Many scientist/founders of the dedicated biotechnology companies have been replaced by managers geared to getting products to markets rather than out of the laboratory (3).

Different sectors of the biotechnology industry also have differing personnel needs. The educational requirements for a position in plant genetic engineering are very different from those for a position in developing monoclonal antibody test kits. The research scientists involved must know different biological systems, and the technicians involved must be familiar with different lab procedures and equipment.

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[1] The overall mean number of employees per biotechnology company (85.9) times the number of companies (296) gives a slightly higher number (25,426) than given here. However, the presence of a few large companies probably skews the average too high. OTA instead multiplied the number of small companies (112) times the average number of employees (11.1), the number of medium companies (121) times the average number of employees (55.3), the number of large companies (56) times the average number of employees (267), and the number of unclassified companies (17) times the overall average number of employees (85.9) to arrive at the figure of 24,347. See ch. 5 for a description of the biotechnology industry.

Scientific personnel needs in biotechnology involve a variety of disciplines, including molecular biology, genetics, microbiology, biochemistry, immunology, and several engineering disciplines. Positions within these disciplines range from Research Director to Technician, and qualifications range from a Ph.D. with substantial experience to a bachelor's degree or, possibly, less (box 8-A).

Box 8-A.—Scientific Positions in Biotechnology Companies

Companies engaged in biotechnology-related research and development vary in the positions they offer, the education and experience required for similar positions, and the responsibilities of staff at particular job levels. The job categories described below are intended to give a general idea of the positions existing within the industry.

Scientific/Research Director: Senior manager responsible for multiple biotechnology research disciplines, such as molecular biology, fermentation, and cellular biology. This is the highest scientific level, and thus requires an exceptionally high degree of expertise and many years of research experience. Also of importance are organizational and interpersonal skills, as well as experience in the business community.

Department Director/Research Director: An individual who is responsible for and manages one biotechnological discipline. The position typically requires a Ph.D. degree, with several years of project management experience in a business setting. Organizational and interpersonal skills are important.

Section Manager/Group Leader: Chief scientist responsible for administering and directing the work of a scientific team involved in one specialized discipline or in a project covering several disciplines. Typical education and experience include a Ph.D., postdoctoral work, and teaching or research experience of at least 8 years since receipt of the Ph.D.

Principal Research Scientist: Head scientist responsible for supervising the work of scientists on several projects in one or more special disciplines. Typical education and experience include a Ph.D., postdoctoral work, and 5 to 8 years of teaching or research experience after receipt of the Ph.D.

Senior Scientist: Participating scientist responsible for supervising the work of other scientists on one or two complex projects. Is involved in departmental planning activities and may also participate in several other projects. Typical background includes a Ph.D. and 2 to 4 years of experience or an M.S. and 6 to 8 years of experience.

Research Scientist: Participating scientist in one or two projects, generally in one discipline. Assists in coordinating and assigning work. May be involved in day-to-day planning and in supervising staff. Is able to work independently. Typical education and experience include a Ph.D. and 1 year of experience or an M.S. and 3 to 5 years of experience.

Research Associate: Participating scientist who gives advanced technical assistance on one or more projects and provides limited supervision. May help coordinate project activities according to schedules set by supervisors. Background usually includes an M.S. and 1 to 3 years of experience or a B.S. and 3 to 5 years of experience.

Research Assistant: Individual who assists on a project under the direction of a senior or higher-level scientist. Typical education and experience include an M.S. and no related experience or a B.S. and 2 to 3 years of experience.

Research Technician: Person who assists on a project, usually by carrying out routine scientific work and conducting standardized tests under direct supervision. Typical background includes a B.S. with none to 2 years of experience.

SOURCE: Industrial Biotechnology Association, *Careers in Biotechnology*, Washington, DC, 1987.

Types of Jobs Available

Molecular biologists and immunologists constitute about a third of the research workers in biotechnology (82). Most molecular biologists have focused on animal and bacterial systems because this research is most applicable to human health (13) and most funding for molecular biology has come from the National Institutes of Health. Immunologists are heavily involved in the development of hybridomas to produce monoclonal antibodies. More recently, the employment of plant molecular biologists has been increasing with the redirection of agricultural research toward molecular biological techniques (see ch. 10).

Bioprocess engineers, biochemists, and microbiologists develop methods of producing biotechnology products in large quantities (13). The demand for these specialties will increase as products are readied for production (82).

Microbiologists study bacteria, yeast, and other micro-organisms and identify microbes with particular characteristics for industrial processes (13). Microbiologists also identify optimum growth conditions for micro-organisms and conditions for production of the substance of interest.

Cell culture specialists perform similar functions for plant and animal cells grown in tissue culture. Tissue culture is becoming increasingly important for the production of useful products, and expertise in tissue culture is an increasingly important skill.

Bioprocess engineers design systems to approximate conditions identified by the microbiologist. Bioprocess engineering is related to chemical engineering. One of the main tasks undertaken by bioprocess engineers is the design of fermentation vats (13) and various bioreactors (55) for the micro-organisms that will produce a given product. Biochemists are required for the next stage of production—the recovery, purification, and quality control of a given product. Many high-value products are extremely fragile, making purification a difficult and highly skilled task.

Available Personnel

For the most part, the available supply of life scientists adequately meets personnel needs (2, 45,48,56), though various observers have identified certain specific shortages in areas such as protein chemistry (6,8,20,64), x-ray crystallography (32), bioprocess engineering (34,35,36,39,42,61,81), cell culture (7,81), quality control (21,52), and other aspects of scale-up. Microbial ecologists are also seen as being in short supply (69,74). In general, companies see an ample supply of scientists trained in molecular biology, biochemistry, cell biology, and immunology, since these areas have traditionally been well-funded by the National Institutes of Health (48).

There are about 66,500 Ph.D.s in the biological sciences work force, representing about a quarter of the total of this work force. Master's degree holders represent another one-third of this total, with the rest holding bachelor's degrees (75). The number of bachelor's degrees awarded in the biological sciences peaked in 1976 at 59,000 and has declined since then. About 38,640 bachelor's degrees were awarded in 1984 (75).

In terms of general biological sciences, the work force is well supplied or oversupplied. During the 1980s, unemployment of recent graduates with bachelor's degrees in biosciences has been higher than for other science and engineering fields, except physics. The life sciences in general, and the biosciences in particular, have been oversupplied for several years, relative to demand (79).

Potential Shortages

Shortages in certain emerging fields, such as protein engineering, are largely unavoidable, due both to the difficulty of predicting which fields will have the heaviest demands and the lag time required for educational institutions to gear up for new fields. The expense of new faculty and new equipment prevents institutions from rapidly moving into new areas. In areas with a shortage of researchers, a shortage of university instructors is usually also apparent (32,50). For example, pharmaceutical companies are hiring x-ray crystallographers with expertise in biological molecules from academia at a rate that threatens to undercut both research and training of future crystallographers (32).

A shortage of microbial ecologists has resulted from the increased interest in the purposeful release of engineered organisms into the environment. Until recently, microbial ecology was a relatively obscure field that attracted less money and talent than more glamorous fields such as molecular biology. The Environmental Protection Agency (EPA) has identified ecological risk assessment, ecosystem structure and function, and ecological and toxicological effects as priority areas (77), but EPA does not fund many extramural research and training programs. The National Science Foundation also supports some research, and thus training, in microbial ecology (74).

Predicting future employment needs accurately requires information that is often unavailable. Such predictions are necessarily speculative. A survey of biotechnology firms in the San Diego area indicates that one-third of the bachelor's level employees hired during the next 5 years will work in recombinant DNA. Other areas of high anticipated need include DNA sequencing, separation chemistry, and animal tissue culture (8) (see table 8-2). Personnel specialists at a 1987 meeting of the Industrial Biotechnology Association also pointed to basic recombinant DNA techniques as their biggest training need (37).

A 1984 OTA report said that a potential shortage of highly trained bioprocess engineers in the United States "could be a bottleneck to the rapid commercialization of biotechnology in the United States" (72). **While no such shortage is evident almost 4 years later, biotechnology still has not been used to produce a large number of products and thus there is not yet a heavy demand for bioprocess engineers.** This is at least partly because biotechnology is still largely used to produce high-value, low-volume products. Producing high-volume, low-value products will require more engineering talent for successful scale-up (41). Some industry representatives fear a shortage of bioprocess engineers lies ahead as more products reach the final stage of commercialization (35,36). Shortages of bioprocess engineers have recently been predicted for the 1990s (61). However, most companies contacted by *Genetic Engineering News,* an industry trade journal, did not expect any personnel shortages to develop during the next 5 years (48). Some biotechnology company personnel managers have, however, reported difficulties hiring biochemical engineers at the B.S./M.S. level with cell culture or fermentation experience (38,29).

Table 8-2.—Anticipated Hiring of B.S.-Level Biotechnologists by San Diego Area Biotechnology Firms, 1987-92[a]

Area of work	Number expected to be hired	Percent of total
Recombinant DNA	292	33%
DNA Sequencing	119	13
Animal Tissue Culture	118	13
Separation Chemistry	117	13
Hybridoma Technology	84	9
Virology	52	6
Protein Synthesis	31	4
DNA Synthesis	24	3
Plant Tissue Culture	19	2
Other (e.g., fermentation, animal model development and testing)	29	3
TOTAL	885	

[a] Data represent estimates for 27 organizations based on responses from 15. Numbers are cumulative for the 5-year period.

SOURCE: Sanford Bernstein, San Diego State University, February 1987.

Since 1984, protein chemistry has emerged as a strong need (6,8,20,21,64). The knowledge of making, purifying, and stabilizing proteins to their active form is required, especially in pharmaceutical applications. The need for immunologists has also increased, due to demand in both monoclonal antibody development and in AIDS research.

Whether or not shortages actually materialize will depend on how rapidly biotechnology products are commercialized and how and when universities and their students respond to predicted manpower needs. While a shortage of bioprocess engineers would be a serious bottleneck for the industry, the actual number needed will not be very large. Bioprocess engineering is not labor intensive, and it has been estimated that personnel requirements for bioprocessing, even after firms enter mass production, will be only 10 to 15 percent of the total biotechnology work force. Furthermore, technological advances, such as biosensors and computer-controlled continuous bioprocessing, could reduce labor intensity (46,72,78).

Potential projected personnel shortages might also be ameliorated by mobility among disciplines. For example, potential shortages of plant molecular biologists were identified several years ago (39,57,72). However, the field of plant molecular biology has been able to move ahead quite rapidly in the last few years due to the large pool of molecular biology postdoctoral fellows and

Photo credit: Calgene

Cell and tissue culture methods are used to regenerate plant cells containing foreign genes into whole plants.

trainees. While many of these scientists were trained in animal or bacterial systems, they were able to apply their skills and knowledge of molecular genetics to plant systems. The postdoctoral pool has thus served as a buffer, although there is still a strong need for biotechnologists with plant expertise (5).

No such postdoctoral pool exists for bioprocess engineering. The current soft market for petrochemical engineers creates a logical pool of potential bioprocess engineers, should shortages become acute. However, traditional chemical engineers have no understanding of living systems. As one engineering professor put it, "When you've spent your whole career with nonliving systems, you just don't get an appreciation of living systems overnight" (14).

Experience in the pharmaceutical industry has shown that chemical engineers can be retrained in bioprocess engineering (72). However, some industrialists argue that large-scale fermentation and downstream bioprocess engineering for recombinant organisms are radically different from traditional biochemical engineering techniques and require special training. For example, recombinant organisms are often fragile and slow producers. Since slow producers are at greater risk of being overrun by contaminants, special techniques to maintain pure cultures are needed (61). In addition, pharmaceutical production is rapidly changing from bacteria and yeast fermentation to mammalian cell culture, which requires different expertise.

Universities have responded with some increased emphasis on bioprocess engineering, although new biotechnology programs emphasize engineering less than genetic manipulation techniques (see "New Initiatives in Biotechnology Training," below). College students appear to be highly responsive to market signals (73) and can thus be expected to seek out educational programs for various aspects of biotechnology to the extent that they perceive occupational rewards from careers in particular areas.

Belief is widespread that interdisciplinary training should be increased, although opinions vary on the specific disciplines that should be included (16,23,40,72). Industrialists have referred to the need for "life-science-oriented engineers and engineering-oriented life scientists" (61), as well as for chemical engineers with an understanding of biosynthesis and biologists with an appreciation for scale-up problems.

Different types of firms have different personnel needs. Generally, smaller firms have a higher percentage of Ph.D. scientists than do larger firms (24). Small firms are more likely to be concentrating on relatively basic research and development, and thus have more Ph.D. research scientists. Small firms are also less likely to be involved in large-scale production, and thus can be expected to have less need for technicians than larger companies. Some analysts have indicated that small companies are less able to afford on-the-job training and need someone who can get up to speed right away (68). Others have indicated the importance of a broad general education, adding that special skills and protocols must be learned on the job (15). The average firm size is increasing (table 8-3), indicating that more firms will need a variety of non-Ph.D. support personnel in both scientific and nonscientific areas.

Table 8-3.—Number of Scientific Employees per Biotechnology Firm, 1983-87

Year	Scientific and Technical Employees per firm	Ph.D.s per firm	Percent Ph.D.s in scientific work force	Source
1983	22.8	12	53	Office of Technology Assessment
1985	42.12	16	37	Institute of Medicine
1987	42.9	12	28	Office of Technology Assessment

SOURCE: Office of Technology Assessment, 1988.

EDUCATION AND TRAINING FOR BIOTECHNOLOGY

Many academics and industry observers believe that the best preparation for biotechnology is training in a traditional discipline, such as genetics or plant physiology, while learning some of the tools of biotechnology. Individuals trained in targeted disciplines can then work in interdisciplinary teams on specific problems. For example, David Pramer, director of the Waksman Institute of Microbiology at Rutgers University, wrote in 1983 that:

> . . . it would be unwise for universities to offer educational programs in biotechnology that are narrowly conceived or overly professional, and it is essential for university scientists within traditional academic disciplines not to abdicate a responsibility to educate biotechnologists . . .
>
> To continue to flourish, biotechnology must be nourished by a steady supply of individuals who also are well educated in traditional disciplines . . . Since biotechnology 5 years from now may be quite different from what it is today, the key to educating a biotechnologist is flexibility in specialized aspects of a program that is firmly based in science and engineering (60).

Many academics believe that new initiatives in training and education are required by the Nation's colleges and universities to meet the education and research needs of the emerging biotechnology industry. OTA identified 60 new initiatives in biotechnology training at 49 different U.S. colleges and universities. These programs are listed in appendix C. Forty-one of these programs responded to an OTA survey requesting information about curriculum, funding, age, number and type of students, and resources of the programs. Results of the survey give a good indication of how colleges and universities have responded specifically to new opportunities in biotechnology and should be representative of *new* initiatives in biotechnology on the Nation's campuses. No attempt was made to catalog the many traditional programs that also provide education and training related to biotechnology. The identified programs range from 2-year applied associate of science degrees to short courses in particular biotechnologies designed for professional scientists. Also included in the OTA list of new initiatives in biotechnology training and education are university-based biotechnology research centers. While these centers generally do not sponsor courses or grant degrees, they do enhance biotechnology education on their campuses through access to equipment, faculty development, and research opportunities for both graduates and undergraduates. These centers also provide a focal point for discussions of how best to educate and train new biotechnologists.

For the most part, university programs have been developed at the institutional level with little or no coordination or formal interaction among the program developers at different colleges and universities. Most do, however, have some form of interaction with industry. Only 7 of 41 programs said that they did *not* consult industry in establishing their programs. Consultations with industry included surveying local biotechnology companies and sending program proposals to industry representatives for comments. While it is generally too early to assess industry's satisfaction with graduates of these programs, most graduates have apparently had a relatively easy time finding employment in their fields.

Age of Programs

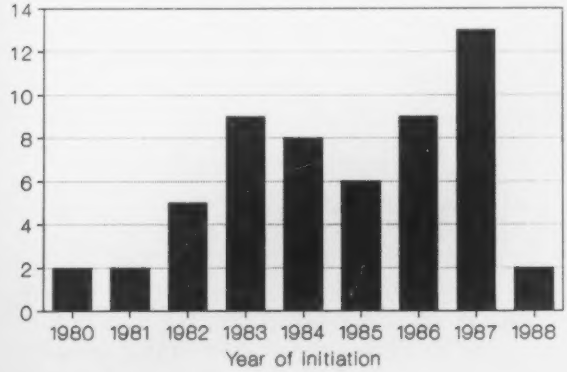
With the exception of programs in biochemical engineering, all of the programs identified are new: the oldest began in 1980. Of 56 programs for which the year of initiation is known, more than a third were begun since 1986 or are still in the planning stage (figure 8-1). Additional programs are probably in the planning stages and may be created in the next few years.

As figure 8-1 indicates, a large number of biotechnology programs were initiated in 1983. This would indicate a 2-year lag from the year when more biotechnology companies were founded, 1981 (see ch. 5). Two years is a relatively short time in which to develop curricula and approve programs, indicating that some institutions moved quickly into biotechnology (28) or at least to identify themselves with biotechnology.

There is no clear pattern of which degree level programs were founded first. In each year a mix of programs was initiated, aimed at a variety of educational levels. For the most part, community college programs are newer than bachelor's and master's programs.

At the doctoral level, most programs are in bioprocessing or biochemical engineering, except for the Iowa Biotechnology Training Program's Ph.D. in microbiology and immunology. Traditional Ph.D. programs in molecular biology, microbiology, biochemistry, and other fields relevant to biotechnology were not surveyed.

Figure 8-1.-University Initiatives in Biotechnology Training[a]



[a] The total number of programs shown here is 56. Biochemical engineering programs are not included.

SOURCE: Office of Technology Assessment, 1988.

Curriculum Content

Recombinant DNA techniques formed the core of many of the programs. Of 32 programs that provided OTA with curriculum information, 26 reported coursework in recombinant DNA. No other specific skill or technology was mentioned by more than half of the programs. Courses or skills mentioned as requirements or electives by one-third to one-half of programs include tissue culturing, hybridoma technology, immunochemistry, bioprocess engineering, fermentation, and purification and separation sciences.

The extent to which training in bioprocess engineering is available is not clear. Only a few programs have in-depth faculty expertise; most expertise is scattered among chemical engineering

Photo credit: Case Western Reserve University

Two undergraduate students read a DNA sequence on an autoradiograph. Such opportunities were extremely rare at the undergraduate level several years ago, but are becoming increasingly common.

departments (14). According to the National Research Council, fewer than 20 U.S. colleges and universities have meaningful biochemical engineering programs (55). The American Council of Education reported in 1985 a total of 58 doctoral engineering programs in biotechnology (33). While many of these programs were in departments of chemical engineering and so most likely relevant to OTA's definition of biotechnology, many others were in departments such as biomedical engineering, which have less relevance to industrial biotechnology.

The currently depressed market for chemical engineering graduates may make it difficult for departments to add faculty, courses, and equipment for bioprocess engineering. If departments have fewer students, they will have some difficulty securing the additional funds. Deciding which, if any, areas of traditional chemical engineering to deemphasize is problematic.

The vast majority of the undergraduate chemical engineering curriculum is mandated by the accreditation standards of the American Institute of Chemical Engineers and the Accreditation Board for Engineering and Technology. At the University of Iowa, for example, students interested in biochemical engineering are urged to use their limited electives for courses in biochemistry, microbiology, biochemical engineering, genetics, and biology. They have also integrated bioreactors, microbial kinetics, and enzyme reactions to illustrate concepts and techniques in traditional chemical engineering coursework (86).

All of the training programs are laboratory-intensive, except for some of the short courses and workshops. Academic program directors who had contacted industry representatives about their needs uniformly reported that industry needed technicians with hands-on laboratory experience and have designed their programs accordingly.

Many biotechnology academic programs reported that a shortage of protein chemists existed in the industry, or that industry needed technicians and bioprocess engineers with an understanding of protein chemistry. No course specifically in protein chemistry was evident in the curricula supplied to OTA, but nearly every program required courses in biochemistry, which would include protein chemistry. It is not clear the extent to which students will learn the solution properties of proteins, purification and sequencing methods, and protein synthesis within these programs. A course in protein chemistry was recommended in a model curriculum for a 2-year program for biotechnicians (see table 8-4). San Diego State University, however, will initiate a Certificate in Protein Engineering in the fall of 1988, which will include specific courses in protein engineering (22). The California State University at Los Angeles intends to offer a course in advanced protein chemistry (66).

Table 8-4.—Biotechnology Programs Offering Associate of Applied Science Degrees

Year of initiation	University	Program
1983	Monroe Community College	Biotechnology Program
1986	Central Community College	Biotechnology Program
1986	State University of New York, Alfred	Biotechnology Program
1986	Technical College of Alamance	Biotechnology
1987	Boston University/Metropolitan College	Biotechnology Laboratory Methods
1987	Madison Area Technical College	Biotechnology Laboratory Technician Program
1988	Becker Junior College	Biotechnician Program

SOURCE: Office of Technology Assessment, 1988.

Community College Laboratory Technician Programs

The need for biotechnicians with specialized but limited training has prompted several community colleges to institute or consider instituting biotechnology training programs. Early in the development of biotechnology, most work was done by highly educated, innovative thinkers, who often had to develop new procedures as their research progressed. As with all technologies, as biotechnology matured, more of the work has become routine and can be assigned to less highly trained technicians (9,62). Figure 8-2 gives a profile of skills

Figure 8-2.—Biotechnology Laboratory Technician Profile

	DUTIES	TASKS								
A	COMMUNICATION	1 Follow and analyze protocol	2 Keep accurate records	3 Communicate subject matter professionally	4 Write reports	5 Organize and present oral reports	6 Locate and review reference materials	7 Read current scientific journals	8 Maintain mathematical literacy	9 Maintain computer literacy
B	SAFETY	1 Identify first aid supplies, personnel and emergency protection areas	2 Maintain safe work area	3 Use appropriate safety procedures and guidelines	4 Label all materials	5 Store and dispose of hazardous materials	6 Monitor handling of radioisotopes and biohazards			
C	MEDIA PREPARATION	1 Practice aseptic techniques	2 Prepare glassware	3 Perform mathematical calculations	4 Make stock reagents	5 Monitor physical properties of a solution	6 Sterilize reagents	7 Dispense media	8 Maintain reagent integrity	
D	FERMENTATION	1 Identify and quantify microorganisms	2 Isolate and maintain pure cultures	3 Maintain and analyze fermentation materials	4 Maintain, analyze and troubleshoot fermentation equipment	5 Prepare seed inoculum	6 Control and monitor fermentation equipment	7 Harvest microorganisms	8 Recover effluent products	
E	TISSUE CULTURING	1 Isolate and characterize cell lines	2 Propagate animal tissue	3 Propagate plant tissue	4 Use cryogenic techniques	5 Perform tissue instrumentation	6 Propagate and harvest viruses	7 Generate monoclonal and polyclonal antibodies		
F	PRODUCT ANALYSIS	1 Evaluate all production materials	2 Evaluate biological characteristics	3 Perform instrumental analysis	4 Perform animal bioinstrumentation	5 Document product specifications	6 Perform statistical and data analyses	7 Maintain and troubleshoot analytical instruments	8 Meet government and/or company standards	
G	GENETIC ENGINEERING TECHNIQUES	1 Construct DNA library	2 Probe and analyze DNA library	3 Construct recombinant vectors	4 Transform host cells	5 Perform mutagenic techniques	6 Apply selective pressures	7 Micromanipulate embryos		
H	NUCLEIC ACID ISOLATION AND ANALYSIS	1 Disrupt cells chemically	2 Ultra centrifuge nucleic acids	3 Analyze by restriction mapping	4 Run DNA gels	5 Perform Northern and Southern blots	6 Label nucleic acids	7 Sequence nucleic acids	8 Synthesize nucleic acids	9 Manage sequence database
I	PROTEIN PURIFICATION	1 Homogenize cells	2 Run protein gels	3 Perform Western blotting	4 Denature/renature proteins	5 Precipitate/solubilize proteins	6 Chromatograph proteins	7 Concentrate (filter and dialyze) proteins	8 Modify proteins	9 Perform enzyme activity assays

SOURCE: Madison Area Technical College, 1987.

required by biotechnicians. Two-year training programs may be appropriate for these technicians (62).

OTA has identified seven associate of applied sciences (AAS) programs in biotechnology, six taught at community or junior colleges and one taught at a state college (table 8-4). These programs are designed to fill the need for biotechnicians, (similar to the more established need of chemical technicians), although students from these programs may go on to 4-year colleges. Six of the seven programs began since 1986, and the seventh began in 1983.

The need for biotechnicians at the AAS level is not well established, but several analysts expect it to surface soon (9,62) based on the precedent from other high-technology industries. A consortium of 2-year postsecondary schools commissioned a study in 1986 to assess the need for 2-year biotechnician training (62). Table 8-5 shows a model 2-year curriculum in biotechnology developed as part of this study.

The 1986 study included a survey of biotechnology companies and a Biotechnology Task Force on Education, consisting of industry and academic members. The study produced a number of significant findings, among them:

- technicians in biotechnology will be different from current technicians in other technology fields, most significantly in that they will require a broader and more interdisciplinary technical base;
- 77 percent of the biotechnology companies surveyed expected biotechnicians to have at least a bachelor's degree; however, since few 2-year programs currently exist, the industry has little experience for judging the quality of 2-year program graduates;
- based on the biotechnology industry's present level of employment of biotechnicians from 2-year training programs, about 200 graduates a year should be able to find placement from 1986 to 1995.
- 2-year programs should be initiated in areas with the largest markets for biotechnicians, which currently includes California, Massachusetts, New Jersey, New York, and Maryland. The need for biotechnicians exists in other parts of the country, however, and will expand as the industry expands.

Industry appears skeptical toward the 2-year programs thus far. Concerns include whether 2 years in college can provide the knowledge necessary to manage complex instrumentation and sensitive organisms (84) and that technicians without a theoretical understanding may not be able to adapt to the changing needs of rapidly evolving technology (84).

Industry representatives also give these reasons for skepticism: a current oversupply of B.S. and M.S. degreed biologists available for technician work; 2-year programs lack the breadth and depth of 4-year programs; and companies need the research background provided by B.S. and M.S. programs (62).

Some reasons for reluctance in hiring graduates of 2-year programs will dissipate as the dedicated biotechnology companies grow and mature. For example, small companies are more likely to require their employees to assume multiple duties, some of which will require more training than 2-year programs provide. As a company's overall

Table 8-5.—Proposed Two-Year Curriculum in Biotechnology

Year One	Year Two
Quarter 1	*Quarter 4*
Introduction to Biotechnology	Industrial Microbiology
Technical Math I: Algebra/Geometry	Computer Operations
Chemistry I: Inorganic	Fundamentals of Instrumentation and Control
Molecular and Cell Biology I	Analytical Chemistry
Technical Communications I	Fluid Power Devices
Quarter 2	*Quarter 5*
Technical Math II: Statistics/Precalculus	Applied Genetics
Applied Physics I	Instrumental Analysis
Molecular and Cell Biology II	Economics in Technology
Chemistry II: Organic	Biotech Internship or Project
Technical Communications II	Mechanical Devices and Systems
	Elective
Quarter 3	*Quarter 6*
Principles of Microbiology	Protein Chemistry
Biochemistry	Industrial Instrumentation
Applied Physics II	Industrial Relations
Electronics	Biotech Project or Internship
Elective	Technical Elective

SOURCE: B.F. Rinard, *Education for Biotechnology* (Waco, TX: Center for Occupational Research and Development, 1986).

workload and staff increases, it can divide tasks by level of skill and may be able to employ people full-time at the lower skill levels. Also, as work continues to shift from research and development to production, more of the tasks will become routine. Larger companies may also be able to afford more time for on-the-job training.

College and University Bachelor's Level Biotechnology Programs

At least 11 colleges and universities have instituted new bachelor's-level programs in biotechnology (table 8-6). Like the 2-year programs, these programs emphasize hands-on laboratory experience, but include more theoretical science and humanities courses. Students are prepared either to go directly to work in industrial labs, or to enter master's or doctoral programs.

The Rochester Institute of Technology (RIT) instituted its biotechnology program in 1983 "to prepare graduates to work as biotechnologists in research programs and development and production facilities in academia, government, private industry, and other organizations" (28). Students also go on to M.S. and Ph.D. programs. In addition to courses in general biology, chemistry, biochemistry, and molecular biology, the program requires 25 courses related to biotechnology, including specific courses on analytical chemical separations, mammalian tissue culture, plant tissue culture, hybridoma techniques, plant physiology, genetic engineering, and an individual biotechnology senior research project. Students are also encouraged to work in a cooperative education program for four quarters, making the course of study a total of 5 years instead of 4. Employers in the cooperative education program have included government, industry, and academic labs.

Although it is among the oldest of the new initiatives in biotechnology education, the RIT program has only 45 graduates (as of spring 1988), due to the length of time required to complete the program.

Like many of the programs identified, the RIT program consulted with industry during program planning and implementation. RIT established a Biotechnology Advisory Council, consisting of representatives of 12 companies with interests in biotechnology. The head of the Department of Biology at RIT reports that council members "continue to be involved in curriculum review in light of the rapidly changing needs of the field, (and) in providing up-to-date information about their companies' particular interests and needs" (28).

Another program in New York State is the bachelor of science degree in recombinant gene technology offered by the State University of New York College at Fredonia. In addition to general courses in chemistry, biology, botany, and physics, the program requires courses in recombinant gene technology, genetics, and cell and subcellular biology. Initiated in 1983, the program had 43 stu-

Table 8-6.—Biotechnology Programs Offering Bachelor of Science Degrees

Year of initiation	University	Program
1980	State University of New York, Plattsburgh/W.H. Miner Agricultural Center	In Vitro Cell Biology and Biotechnology
1982	Worcester Polytechnic Institute	Biotechnology
1983	Cedar Crest College	Genetic Engineering
1983	Rochester Institute of Technology	Biotechnology
1983	State University of New York, Fredonia	Major in Recombinant Gene Technology
1984	Case Western Reserve University	Concentration in Biotechnology and Genetic Engineering
1986	California Polytechnic State University	Biochemical Engineering
1986	Cook College, Rutgers University	Biotechnology[a]
1986	North Dakota State University	Biotechnology Academic Program
1987	University of Kentucky	Biotechnology
1988	Ferris State College	Biotechnology Emphasis

[a] Curriculum is pending approval by the State Department of Higher Education.

SOURCE: Office of Technology Assessment, 1988.

dents enrolled in the spring of 1988. A total of 44 students had completed the program through 1986, with most going to work in academic or government laboratories.

The oldest bachelor's level biotechnology program identified by OTA is the In Vitro Cell Biology & Biotechnology Program, begun in 1980 by the State University of New York at Plattsburgh and the W.H. Miner Agricultural Center. The program includes both an approved major field of study at Plattsburgh leading to the bachelor of science degree and a self-contained semester of intensive training in techniques of biotechnology. One semester of the B.S. program consists of a 15-credit-hour course of lecture and laboratory work in tissue culture and biotechnology in residence at the Miner Institute. This course is also open to qualified students from other colleges and universities, and attracts both undergraduate and postbaccalaureate students.

The North Dakota State University at Fargo offers a bachelor of science degree in biotechnology in both its College of Agriculture and its College of Science and Mathematics. A minor in biotechnology is also available. In addition to traditional courses, North Dakota State offers courses in recombinant DNA, plant cell and tissue culture, animal cell culture, plant micropropagation, and process biochemistry. Having begun in 1986, the program has no graduates yet.

The University of Iowa offers B.S. as well as M.S. and Ph.D. degrees in chemical and material engineering with opportunities in biochemical engineering/biotechnology. The Iowa program prepares its B.S. students primarily for M.S. and Ph.D. programs.

Other existing or planned B.S. level programs in biotechnology include those at Cook College of Rutgers University, Ferris State College in Michigan, the University of Kentucky in Lexington, and Cedar Crest College in Allentown, Pennsylvania.

Certificate Programs

Certificate programs are offered to postbaccalaureate students who wish to learn specific techniques in biotechnology (table 8-7). Four universities in the California State University system offer certificates in biotechnology or related technologies to either undergraduate or postbaccalaureate students in the life sciences. Other universities offer certificates at the graduate level.

Photo credit: Rochester Institute of Technology

An undergraduate student majoring in biotechnology prepares DNA for restriction enzyme mapping.

Two of the most established programs are at San Diego and San Francisco State Universities, both initiated in 1983. San Diego offers a certificate in recombinant DNA technology as well as an M.S. in molecular biology and a Ph.D. in molecular and cellular biology. The certificate program consists of 24 semester units of courses in radioisotope techniques, biochemistry, bacterial genetics, molecular biology, and recombinant DNA techniques. An internship in a university or industrial laboratory is also required. San Diego State Univer-

Table 8-7.—Programs Offering Certificates in Biotechnology

Year of initiation	University	Program
1980	W.H. Miner Agricultural Center	In Vitro Cell Biology and Biotechnology
1983	San Diego State University	Recombinant DNA Technology
1983	San Francisco State University	Genetic Engineering
1986	California State University at Hayward	Biotechnology
1986	Rutgers University	Biotechnology
1986	Tufts University	Training Program in Biotechnology Processing
1987	California State University at Los Angeles	Biotechnology
1988	San Diego State University	Protein Engineering
Planned	San Diego State University	Agricultural Biotechnology

SOURCE: Office of Technology Assessment, 1988

sity will offer a Certificate in Protein Engineering starting in Fall 1988, and plans to start offering a Certificate in Agricultural Biotechnology in Fall 1989 (22).

San Francisco State University offers a similar program. The Genetic Engineering Certificate Program is open to postbaccalaureate students "who wish to become specifically competent in the concepts and laboratory skills of genetic engineering" (65). The 13 units required for the certificate may be used toward the 30 units required for the master's of science in biology. About 50 people have completed the certificate program, and about three-fifths are working for biotechnology companies. The remainder are working in university laboratories or are pursuing graduate degrees.

California State University at Hayward initiated a certificate program in biotechnology in 1986. The program requires one academic year to complete 28 quarter units of work in cell biology, molecular cloning, immunochemistry, cell culture, radiation biology, and other electives. Developers of the Hayward program consulted biotechnology companies and identified industry needs in protein purification, immunochemistry, and cell culture.

California State University at Los Angeles started a 1-year certificate program in biotechnology in the fall of 1987, which can be applied to a master's degree program. The core of the program consists of four courses in gene manipulation. The program developers anticipate adding courses in hybridoma laboratory techniques, cell culture, and advanced protein chemistry. The program director visited four biotechnology companies and heard the following needs expressed: employees who bring their minds as well as their hands to a task; employees who have had research project experience of at least half-time intensity; and employees with expert theoretical backgrounds in protein chemistry (66).

A similar although shorter program is the Training Program in Biotechnology Processing offered by the Biotechnology Engineering Center of Tufts University. Tufts offers this 15-week summer program designed to train students in biotechnology processing, and to place them in positions as technicians in industry. Sponsored by Tufts and a consortium of biotechnology companies, the program received start-up funds from the Bay State Skills Corporation.

Rutgers University offers a certificate in biotechnology to its M.S. and Ph.D. students in the Departments of Microbiology and Chemical and Biochemical Engineering. In addition to the degree requirements of their programs, students in the certificate program must complete 15 credits from a list of courses in biotechnology, such as Chemistry of Microbial Products and Enzyme Engineering. For students in either the microbiology or the chemical and biochemical engineering program, at least six credits must be taken outside of the program in which the student is registered (59).

University Master's Level Biotechnology Programs

Master's degree programs in biotechnology are multidisciplinary and often interdepartmental (table 8-8). Almost all the programs preparing students for careers in bioprocessing are at the

Table 8-8.—Biotechnology Programs Offering Master of Science Degrees

Year of initiation	University	Program
1955	Massachusetts Institute of Technology	Biochemical Engineering
1970	Rutgers University	Biochemical Engineering
1980	State University of New York, Plattsburgh/Miner Institute	In Vitro Cell Biology and Biotechnology
1981	University of Maryland, Baltimore County	Applied Molecular Biology
1982	Worcester Polytechnic Institute	Biotechnology
1984	Case Western Reserve University	Concentration in Biotechnology and Genetic Engineering
1984	University of Minnesota	Microbial Engineering
1985	University of Iowa	Biochemical Engineering/Biotechnology
1985	University of Tennessee, Knoxville	Biotechnology
1986	California Polytechnic State University	Biochemical Engineering
1986	Tufts Biotechnology Engineering Center	Biotechnology Engineering
1987	Lehigh University	Applied Biological Sciences
1987	Old Dominion University	Biotechnology
1988	University of Illinois	Biological Engineering
Planned	San Diego State University	Biotechnology
Planned	University of South Florida	B.S./M.S. in Biotechnology

SOURCE: Office of Technology Assessment, 1988.

master's and doctoral levels, and several directors of these programs indicated that industry considered M.S. and Ph.D. degrees to be the entry level in bioprocessing (63,86). The need to combine process engineering with a basic understanding of molecular biology requires advanced training, according to some observers (27,71,86).

The University of Maryland, Baltimore County, has offered a master's degree in Applied Molecular Biology since 1981, with the first class graduating in 1984. The degree can be earned either in a 2-year postbaccalaureate program or as a 5-year B.S./M.S. program. Emphasizing hands-on laboratory skills, the program requires a summer research internship. A Ph.D. program in Molecular and Cellular Biology that will use the Applied Molecular Biology program as its core curriculum is under development.

Lehigh University in Bethlehem, Pennsylvania, is establishing an M.S. in applied biological science, which will provide students with hands-on experience in genetics, biochemistry, and bioprocessing. While preparation for a Ph.D. program is the principal goal of the program, students will also be prepared to work for industry. The program is sponsored by the Biology, Chemistry, and Chemical Engineering departments.

The University of Minnesota offers a master's degree in microbial engineering, which will enable students to integrate the basic science of microbiology with technological applications of the capacities of micro-organisms, cultured cells, and parts thereof. The interdisciplinary program draws on faculty from more than nine departments of four colleges and institutes in the university. Begun in 1984, the first five students finished in 1987.

San Diego State University is in the process of establishing a different type of master's program, which will combine scientific instruction with corporate and legal instruction. The program will have tracks in biopharmaceutical toxicology/risk assessment, venture capital and entrepreneurial biotechnology business development, and regulation and biotechnology patent law (22).

Tufts University has a 5-year B.S./M.S. program in chemical/biochemical engineering. The program includes all the courses required for certification as a chemical engineer plus courses in cell and microbe cultivation, biotechnology processing lab, applied enzymology, and biochemical engineering. Core courses are given in the early evening, making them accessible to people in industry.

Doctoral Programs

Traditional doctoral programs in biological, chemical, and engineering sciences produced the expertise that created today's commercial opportunities in biotechnology. Nonetheless, OTA did not attempt to evaluate or catalog these programs, as they are well developed and have mature professional societies and accreditation systems in place.

Academic opinion is divided about the desirability of creating new doctoral programs in biotechnology. Increasingly, biotechnology is viewed as comprising a set of tools that can be applied to a variety of disciplines. On the other hand, biotechnology increasingly requires interdisciplinary training or at least the ability to collaborate effectively across disciplines.

Several doctoral programs are making biotechnology an explicit component of their curricula and Ph.D.s in biotechnology are under consideration (table 8-9). Case Western Reserve University offers a Ph.D. in biology with a concentration in biotechnology and genetic engineering. At the University of Minnesota, a Ph.D. minor in Biological Process Engineering is under development. And the University of Maryland, Baltimore County, is developing a Ph.D. program in Molecular and Cellular Biology that will use courses in applied molecular biology as its core curriculum. Several universities offer Ph.D.s in biochemical engineering.

In many areas of the life sciences, biotechnology companies are well supplied with Ph.D. scientists (38). The greatest need at the Ph.D. level is biochemical and bioprocess engineering (55).

Short Courses in Biotechnology

Short courses in biotechnology, ranging from a couple of days to a couple of weeks, are a popular way for scientists of various backgrounds to learn a particular technique (table 8-10). Shorter workshops may be centered around lectures and demonstrations, and longer workshops will usually have hands-on laboratory components.

Begun in 1982, the Center for Advanced Biotechnology Training in Cell and Molecular Biology at the Catholic University of America in Washington, D.C., has one of the most established series of short courses. Participants are usually mature scientists seeking information and skills to assist them in research and, to a lesser extent, in teaching (53). The Center has trained about 1,200 scientists in areas such as immunochemistry, hybridoma/monoclonal antibody production, tissue culture, recombinant DNA methodology, protein sequencing, and separation techniques. Courses are funded entirely by tuition.

Rutgers University in New Jersey also offers a variety of short courses related to biotechnology. Demand from industry for these courses is high, with students coming to New Jersey from California and Europe to participate (60). Tufts University and Worcester Polytechnic Institute both offer short courses in bioprocessing for university-level instructors.

University Biotechnology Centers

University-based biotechnology research centers take many forms and have varied purposes. Examples of centers include the Center for Bioprocess Engineering at MIT, the Biotechnology Program at Cornell, the Center for Biotechnology at the State University of New York at Stony Brook, the University of Wisconsin Biotechnology Center, and the Penn State Biotechnology Institute. The Ohio State University is in the process of establishing a biotechnology center. (See ch. 4 for an extensive listing of biotechnology centers.)

Table 8-9.—Biotechnology Programs Offering Ph.D. Degrees

Year of initiation	University	Program
1955	Massachusetts Institute of Technology	Biochemical Engineering
1970	Rutgers University	Biochemical Engineering
1982	North Carolina State University	Minor in Biotechnology
1984	Case Western Reserve University	Concentration in Biotechnology and Genetic Engineering
1985	University of Iowa	Emphasis in Biochemistry/Biotechnology
1986	Tufts University	Biochemical/Chemical Engineering
1987	Lehigh University	Biochemical Engineering
Planned	University of Illinois, Urbana/Champaign	Biological Engineering
Planned	University of Minnesota	Minor in Biological Process Engineering

SOURCE: Office of Technology Assessment, 1988.

Table 8-10.—Biotechnology Programs Offering Short Courses[a]

Year of initiation	University	Program
1982	Catholic University of America	Center for Advanced Training in Cell & Molecular Biology
1983	American Type Culture Collection	Workshops
1983	State University of New York, Stony Brook	Biotechnology
1984	Cook College of Rutgers University	Biotechnology
1985	University of Minnesota	Institute for Advanced Studies in Biological Process Technology
1986	Tufts University	Biotechnology Engineering Center

[a] Many institutions offer summer and other short courses in fields related to biotechnology. This list is only representative of some of the more established or better known programs.

SOURCE: Office of Technology Assessment, 1988.

Purposes of the centers frequently include conducting or sponsoring research, coordinating biotechnology research and training among the various university departments, providing a forum for multidisciplinary projects, and purchasing specialized equipment. Centers may also be involved with local biotechnology companies in technology transfer and economic development activities. Some centers sponsor short courses in laboratory techniques for both academic and industrial scientists.

Only two of the biotechnology centers contacted by OTA said their sole function was research. All the others reported that some portion of their mission (usually 10 to 35 percent) was for training and education.

Founded in 1981, the Program in Molecular Biology and Biotechnology at the University of North Carolina at Chapel Hill is one of the oldest programs of its kind. The program sponsors workshops and conferences designed to give researchers intensive hands-on experience in DNA technologies. The program also supports core facilities important for research and training in biotechnology and molecular biology. They state their primary purpose as "facilitating the diffusion of molecular technology throughout the biological community." Together with the North Carolina Biotechnology Center, the program sponsors a university/industry cooperative research center in monoclonal lymphocyte technology (25).

The Center for Biotechnology at the State University of New York at Stony Brook supports "programs for research and education to stimulate a university/industry partnership and economic development" (49). Supported by more than 30 different biomedical departments, ranging from chemistry to medicine, the Center sponsors several activities related to training and education. The Center also sponsors a variety of seminars and conferences on biotechnology, including a workshop cosponsored by Cold Spring Harbor Laboratory in molecular biology for secondary school science teachers. The Center also provides financial support for SUNY students to work in biomedical laboratories.

The University of Wisconsin Biotechnology Center is involved in a variety of training functions. It has sponsored short courses in biocomputing and sequence analysis and workshops in agricultural biotechnology. The Center is also working with the Biochemistry and Chemical Engineering Departments to develop a Bioprocess and Metabolic Engineering Training Consortium (44).

The Michigan Biotechnology Institute has an institutional relationship with universities. Although it is a free-standing institute, it funds master's, doctoral, and postdoctoral traineeships at Michigan State University, the University of Michigan, and Michigan Technological University.

Other Curricular Components of Biotechnology

New biotechnology is being incorporated into many traditional programs outside of the basic biological sciences, such as chemical engineering, pharmacy, and agriculture.

The University of California at Davis, for example, has no formal curriculum in biotechnology at the graduate or undergraduate level, but does have a Biotechnology Program of the College of

Agriculture and Environmental Sciences to facilitate research and education programs. Discipline-based majors, such as biochemistry, bacteriology, genetics, fermentation science, and engineering, are tailored by the student and his or her advisor with the necessary electives to prepare the student for a career in biotechnology. The Biotechnology Program serves to enrich and extend existing strengths by reviewing curricula and assuring that relevant courses are offered frequently enough.

At San Jose State University, the concentration in biochemistry, begun in 1972, is being modified to reflect new requirements for biochemists. A course in recombinant DNA methods is now included in the chemistry curriculum, and other modifications are being considered. A member of the San Jose State University (SJSU) Department of Chemistry reflects a widely held opinion in saying she would "most like to see biotech methods to be incorporated into already established laboratory courses as opposed to having separate specialty courses." SJSU organized a symposium with representatives of biotechnology firms to determine industry's needs and found that industry was looking for students who are well versed in basic, fundamental principles, and are capable of problem solving and independent thought more than students who are specialized in sophisticated techniques.

Photo credit: Case Western Reserve University

An undergraduate separates myosin and myosin-light-chains, using fast protein liquid chromatography, as part of an undergraduate biotechnology program.

Tufts University has added a course in "Frontiers in Biotechnology" to their chemical engineering curriculum. The course will give chemical engineers an overview of genetic engineering, biotechnology, and hybridoma production, with emphasis on laboratory techniques.

OTA has no figures on the number of universities that have added courses in recombinant DNA and other biotechnologies to traditional majors, but it is probably significant. Many of these courses are new offerings. Until recently, students would not have the opportunity to conduct experiments with recombinant DNA technology until graduate school. Now many of these courses have been introduced to undergraduates and, in some cases, high school students.

Retraining

Retraining has emerged as a significant need given the rapid development of new biotechniques and the large number of researchers who received their formal training before new techniques were widely integrated into biological research. Short courses described previously are a principal way of accomplishing this retraining. In addition, most biotechnology companies, at least the larger ones, provide training funds for their employees. Almost 9 out of 10 (88 percent) of the biotechnology companies surveyed reported that they provide educational assistance to their employees (38).

In addition, retraining is an integral part of many companies' day-to-day operations. Companies hold seminars, sponsor cross-department training, and establish systems to keep their research staffs abreast of current literature (43).

Retraining is also a principal motivation for companies to enter into collaborative arrangements with universities. These arrangements frequently allow company scientists to spend time in university laboratories, updating their skills (see ch. 7).

Biotechnology in Secondary Schools

Gradually, aspects of genetic engineering and other new biotechnology techniques have reached high school classrooms. Several programs such as the Cold Spring Harbor/SUNY Stony Brook workshop mentioned above, have been designed to teach recombinant DNA techniques to secondary school teachers. Over a dozen States are planning biotechnology educational programs for high schools (10).

The North Carolina Biotechnology Center has embarked on a 3-year Secondary Education Project to introduce biotechnology into the high school curriculum. The first group of high school biology teachers was brought to the center in July 1987 to conduct recombinant DNA experiments and to develop lesson plans and materials to teach the science, applications, and social issues of biotechnology. The University of Wisconsin Biotechnology Center also sponsors workshops for high school biology teachers.

Cold Spring Harbor Laboratory sponsors week-long workshops around the country to educate high school biology teachers in recombinant DNA technology. The 3-month project, conducted in 1987, had a goal of reaching 250 teachers. Twice as many teachers applied as could be accepted (19).

The California Sector of the Industrial Biotechnology Association also sponsors training in biotechnology for high school teachers at three centers in the State (1). California has also recently established a Blue Ribbon Biotechnology Curriculum Advisory Committee in order to strengthen the high school biology curriculum (4).

Biological Sciences Curriculum Study, a major publisher of textbooks and learning modules for high school students, is increasing its emphasis on biotechnology in its material. A module due out in spring 1988 covers *Advances in Genetic Technologies* and includes experiments in bacterial transformation and plant crown gall formation (51).

FUNDING OF TRAINING ACTIVITIES

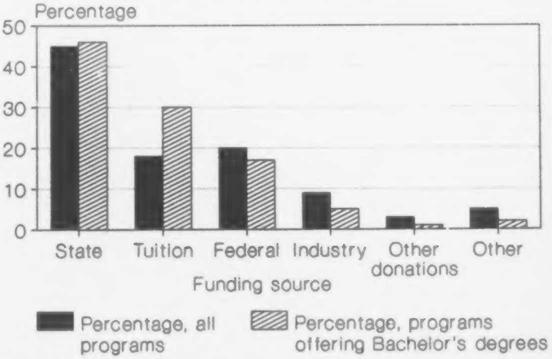
Traditionally, most Federal funding of biotechnology has been directed toward research at major universities. These funds, most of which come from NIH, indirectly support training, though mainly at the graduate and postdoctoral levels. Training at the undergraduate level is supported only to the extent that these funds "trickle down" in the form of making equipment available, providing teaching assistants, and enriching faculty members' abilities to teach subjects related to biotechnology.

States provide a significant amount of funding for education and training in biotechnology. About three-fourths of the programs identified by OTA are at State institutions, and States provide, on average, almost half of the funds for these programs. The Federal Goverment provides about 20 percent of the programs' funds (figure 8-3).

It is difficult and perhaps artificial to completely separate training funds from research funds, as the two activities are closely linked at U.S. universities. Nonetheless, funds are frequently allocated by State and Federal agencies with one or the other purpose in mind. Programs stressing education rather than research or vice versa have different needs, in degree if not kind, so it is useful to distinguish to the extent possible funds intended for education as opposed to funds intended for research.

As biotechnology education has permeated the undergraduate and even secondary school curriculum, sources of funds have become more diversified. Programs responding to OTA's survey reported that significant percentages of their

Figure 8-3.-Source of Funds for Biotechnology Training and Education Programs



SOURCE: Office of Technology Assessment, 1988.

funds came from State and industrial sources, as well as from student tuition. For the 36 programs reporting their sources of funds, State governments supplied the lion's share of support, providing almost half of the funds. Tuition provided the next largest share of funds, just below one-fifth, followed closely by the Federal Government. Industry-sponsored research provided almost 10 percent of program funds (figure 8-3).

The programs are costly due to expensive equipment and materials and generally intensive laboratory work. One State-subsidized program costs about $10,000 per student (84). **Three-fourths of the programs (29 of 41) reported unmet needs for space or equipment.**

Federal Funding

Most of the current cadre of Ph.D. biotechnologists in industry and academia were supported by Federal research or training grants when they were trained in the various disciplines that undergird biotechnology (5). However, few Federal funds are designated specifically for biotechnology training. Most agencies have no formal training program; any training in biotechnology is achieved through the usual grants mechanisms. Most direct Federal support to students goes to graduate students in the form of fellowships, traineeships, and research assistantships. However, Federal support for life sciences is strong, and in 1985, Federal funds were the primary source of support for almost 20 percent of the life science Ph.D.s, compared with less than 8 percent of other science and engineering fields (80). Of 35,980 full-time biological science graduate students, 10,532 received some Federal support in 1984 (80). In the life sciences, enrollment rises with increased Federal support, and drops when Federal support drops. A drop in support since 1980 already is reflected in a drop in the Ph.D.s awarded (80). Six Federal agencies contacted by OTA reported specific efforts in training for biotechnology (see ch. 3 for a full discussion of Federal funding).

National Institutes of Health

The National Institutes of Health is by far the largest Federal supplier of fellowships, traineeships, and training grants, providing 87 percent of the funds for these activities. NSF is a distant second with 9.2 percent of the total (80).

Predoctoral training occurs in many fields and many disciplines directly or indirectly related to biotechnology. Postdoctoral traineeships have been funded by the National Institutes of Health (NIH) at a level of $150 to $170 million per year in recent years. NIH estimates that $70 million in training funds go to students working in areas either directly or indirectly related to biotechnology, mostly at the predoctoral level (83). Most of the funds come from the National Institute of General Medical Sciences (NIGMS). In addition, NIH supports 45 research associates in biotechnology for 1 to 3 years in an NIH laboratory. NIH officials report that the training dollar at NIH has shrunk from 18 percent of the research budget in 1971 to less than 5 percent of the research budget in fiscal year 1988. NIH supports a total of about 12,000 graduate students (80), about half of whom could be expected to be working in areas directly related to biotechnology.

At a 1985 meeting of the NIH Director's Advisory Committee, officials of the White House Office of Science and Technology Policy suggested that NIH support training in biotechnology in all disciplines, including the agricultural and physical sciences. It is not surprising that NIH responded negatively to this suggestion given the agency's strong tradition in the biomedical sciences. A consensus was reached, however, that in order for the United States to maintain a strong lead in biotechnology there must be increased research training in the basic disciplines of biotechnology—molecular genetics, biology, immunology, biochemistry, and virology.

NIH is currently collaborating with the National Science Foundation to support the Massachusetts Institute of Technology Biotechnology Center to enhance research training in bioprocess engineering (see box 3-A). In addition to the predoctoral and postdoctoral fellowships available through the National Research Service Awards Act, the NIH intramural program has recently established a research associateship and a biotechnology fellowship program through which about 40 people will be supported to receive research training in appropriate intramural biotechnology-related laboratories. The average cost is $18,000 to $36,000 a year per individual.

National Science Foundation

The National Science Foundation (NSF) sponsors competitive, peer-reviewed predoctoral fellowships, making 450-540 new 3-year awards each year from an annual appropriation of about $27 million; 25-35 percent of the awards are in the biological and biomedical sciences (55).

At the postdoctoral level, NSF funds about 20 fellows in each of two areas relevant to biotechnology—plant biology and environmental sciences —for a total of $2.2 million per year (55).

NSF also contributes to the Presidential Young Investigator awards, which support outstanding young faculty scientists at a base rate of $25,000 per year for 5 years. In the biological sciences, 25 recipients were named in 1984, 21 in 1985, and 10 in 1986 (55).

Other training funds within NSF are available through the award structure itself, rather than specialized fellowships. However, research grants are estimated to support only 0.3 trainees per grant, due to the small size of most NSF grants (85). NSF also supports biotechnology education through mechanisms such as the Biotechnology Process Engineering Center, which is an NSF Engineering Research Center at the Massachusetts Institute of Technology, and its support of Cold Spring Harbor Laboratories training and outreach programs. Other programs, such as Instrumentation and Laboratory Improvement and Undergraduate Faculty Enhancement, also support training efforts.

Department of Defense

The Office of Naval Research (ONR) supports fellowships run by the National Research Council at a level of about $400,000 annually. Approximately five of the fellowships are in fields related to biotechnology. In addition, many graduate students are supported on contract awards, but it is not clear how many of those are in fields related to biotechnology.

Department of Agriculture

The Food and Agriculture Sciences National Needs Graduate Fellowship Grants program of the Cooperative State Research Service (CSRS) supported 87 doctoral degree candidates in 16 institutions in fiscal year 1986, totaling approximately $1.5 million. Although figures are not available, $45 million in biotechnology research (see ch. 3) provides varying levels of support to a large number of graduate students and postdoctoral fellows. It is difficult to determine the extent to which either of these programs actually supports students working in areas relevant to biotechnology.

In 1984, the U.S. Department of Agriculture initiated a peer-reviewed program of training grants to university departments to support 302 predoctoral students. Approximately 35 percent of the $5 million in training grants were in biotechnology. The same students, who had been guaranteed 3 years of support, received an additional $5 million in 1985, but no new grants could be awarded as no additional funds were available. In 1986, funds were cut to $3 million, thus reducing support for each student. A 1987 appropriation provided $2.8 million dollars, which will be used to fund a new crop of students for the full 3 years, thus substantially reducing the number of awards that can be made (55).

The Agricultural Research Service initiated a competitive postdoctoral program in 1984 that supported 21 people for 1 to 2 years to work on specific projects at ARS laboratories. Award recipients increased to 50 in 1985 and 100 in 1986. The programs' 1986 appropriation was $4 million; about half of the fellowships involved biotechnology (55).

Agency for International Development

Training is an integral part of the AID research programs. Practically every AID-supported research project includes training and networking among the scientists of underdeveloped countries and scientists in the developed world. Training programs range from short workshops to longer, 6-month programs. Graduate training and postdoctoral training is included in many research activities. About one-fifth of all AID research funding is for training and networking, with the exception of the International Agricultural Research Centers, where support for training scientists from lesser-developed countries approximates 7 percent.

Other Federal Agencies

Other agencies provide some training support through various funding mechanisms. The National Oceanic and Atmospheric Administration supports approximately 50 students on 56 projects broadly related to biotechnology. The National Aeronautics and Space Administration supports 50 to 55 graduate and postdoctoral students via grants awarded to universities but has no dedicated money for training. The Food and Drug Administration, Environmental Protection Agency, Veterans Administration, and Department of Energy have no specific programs to support training.

State Funding

States provided about 45 percent of the funds for new initiatives in biotechnology training identified by OTA. Of those States responding to a separate OTA survey (see ch. 4), 17 reported that they directly fund training programs in biotechnology at their State universities and colleges. Not all were able to provide exact dollar figures. In many cases, the State department of higher education provides funds for research and training, under which biotechnology may fall. Because these funds are dispersed to many institutions and many departments within those institutions, accounting for spending specifically on biotechnoiogy training is complex.

Some States, however, were able to report on expenditures for biotechnology training programs. The nature of the programs and the degrees offered were not specified. Of those reporting, expenditures in fiscal year 1987 ranged from $40,000 in Pennsylvania to $1.3 million in Georgia. Others included $250,000 in Connecticut, $500,000 in Iowa, $300,000 in Maryland, $450,000 in Connecticut, $63,000 in New York, and $50,000 in North Dakota. In Massachusetts, funding for biotechnology training must go through the Bay State Skills Corporation, with a requirement for an industry match. The State provided $165,000 in fiscal year 1986 and $75,000 in fiscal year 1987.

Industrial Funding

Industry funding accounted for just under 10 percent of the funds of biotechnology training programs surveyed by OTA. In a 1984 survey, 32 percent of 106 biotechnology firms responding indicated that they provided grants and fellowships to schools and individual trainees (12). Based on that survey, it was estimated that biotechnology companies provided between $8 and $24 million for training grants and scholarships in 1984 (11). In addition to grants and scholarships, approximately 12 percent of trainees at research-intensive universities receive industrial support for their research, and 10 percent receive some industrial contribution to their salary. All together, about 19 percent of trainees receive some direct financial assistance from industry in the form of training grants, scholarships, research support, or salary (31).

Private Philanthropy

The Howard Hughes Medical Institute has recently become a principal sponsor of biological education. In 1988, Hughes will announce grants totaling $30 million to bolster undergraduate sciences at liberal arts and historically black institutions. The awards are part of a new 10-year program that will provide $500 million for education in medical and biological sciences. The institute is also funding education projects at several laboratories and gave the National Research Council almost $600,000 to study high school biology education.

The Institute also plans to award 3-year graduate fellowships (renewable for 2 additional years) to 60 students each year. This year's fellows will receive stipends of $12,300, plus $10,700 for tuition and fees.

SUMMARY AND CONCLUSIONS

For the most part, the supply of specialists in biotechnology seems adequate to meet demand at the present time, though shortages in particular areas are evident. Shortages in cutting-edge areas, such as protein engineering, have occurred, but are largely unavoidable. Anticipated shortages of bioprocess engineers have not yet occurred, but may yet occur as more biotechnology products reach the later stages of commercialization. Demand for expertise in plant and animal tissue culture and protein chemistry is high and may be outstripping supply. A shortage of microbial ecologists has been brought about by the need to assess the risks of releasing engineered microorganisms into the environment. A large pool of postdoctoral fellows and trainees in molecular biology who could shift into new areas has prevented the serious shortages of plant molecular biologists predicted several years ago. Many of these scientists were originally trained in bacterial systems.

Growth in employment in biotechnology has been rapid and will continue, although biotechnology is not expected to generate a substantial number of jobs compared with traditional industrial sectors. The need for specialized biotechnology workers, coupled with time required to train personnel, demands planning for future personnel needs. Current employment trends include greater opportunities for technicians and an increase in demand for bioprocess engineers.

University programs in biotechnology have proliferated in recent years, addressing a variety of educational levels. State sources have provided a large percentage of funds for these programs, and Federal funds have provided a much smaller percentage. Consultation with industry is the rule rather than the exception in the development of biotechnology programs. It is too early to assess the effectiveness of most of these programs or industry's satisfaction with the training students in these new programs have received. Nonetheless, the nation's campuses have clearly moved quickly to establish new initiatives in biotechnology research and training.

Biotechnology programs usually emphasize recombinant DNA techniques. Other aspects of biotechnology, such as plant and animal tissue culture, are common though less frequently found in biotechnology curricula. Bioprocess engineering is less evident in the programs identified by OTA, but is gaining in importance. Bioprocess engineering will often be taught as part of a chemical engineering department, and may be less readily identifiable as biotechnology. Only a few programs explicitly cover bioprocess engineering in depth. Many of the best researchers in the field are scattered at various universities, so few programs are focal points of research and training. While the supply of bioprocess and biochemical engineers has not become a bottleneck for the industry, this area remains a major training need.

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Chapter 9

Investment in Biotechnology Applied to Human Therapeutics

"Biotechnology is in a state of evolution . . . the industry is moving away from the technological phase into the clinical phase."

Peter Drake in *Chemical Week*,
Sept. 30, 1987, p. 20.

"[there are] not many problems with FDA. It takes a long time to get anything approved, but the delays are not unique to biotech products."

unidentified industry spokesman, *Bio/Technology*,
December 1987, p. 1277.

"The equation in biotechnology is becoming all too familiar: patent plus patent equals lawsuit."

(editor) /In The News/ *Bio/Technology*,
December 1987, p. 1251.

"We seem to be at a point in the history of biology where new generalizations and higher order biological laws are being approached but may be obscured by the simple mass of data."

H. Moskowitz and T. Smith
Report of the Matrix of Biological Knowledge Workshop, Santa Fe, New Mexico
July 13 to Aug. 14, 1987.

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Chapter 9

Investment in Biotechnology Applied to Human Therapeutics

INTRODUCTION

The promise of novel pharmaceutical applications has captured most of the attention given to biotechnology in the last decade. Pharmaceutical biotechnology, for the purposes of this report, is defined as the use of recombinant DNA, hybridoma, and related new technologies in the manufacture of human therapeutic products; diagnostics and vaccines are not included under this definition. Although the new biotechnologies have not radically changed the pharmaceutical industry, they have contributed to progress in a number of important product development areas, and have brought about a commitment to research and development (R&D) funding from both public and private sources that greatly exceeds that for any other industry.

Biotechnology has facilitated the development of human therapeutic proteins that are difficult to produce in large quantities by traditional methods such as chemical synthesis or extraction from blood plasma. or tissues. **Recombinant DNA technologies** to combine DNA from one organism with that of another have been used to **clone**, or make copies of, genes that produce proteins with therapeutic potential, and to engineer genes to make proteins that are more stable or active than their natural forms. **Monoclonal antibodies** secreted from **hybridomas** (the cells resulting from the fusion of immortal tumor cells with antibody producing cells from mouse, rat, or human sources) have been developed primarily as diagnostic reagents, but their ability to specifically recognize foreign substances has made their use as human therapeutics possible. Studies of the basic molecular mechanisms governing cell physiology have been greatly enhanced by the tools of biotechnology, and will likely continue to lead to new drug discoveries and increased understanding of the origins of disease. Enthusiasm for the design of a new pharmaceutical from knowledge of the structure of the molecule (e.g., a cell surface receptor protein) upon which it acts—often called **rational drug design**—has also been renewed by advances in methods to determine the three-dimensional structures of proteins. Such progress has been spurred in part by the fact that recombinant DNA technology has increased the availability of previously scarce human proteins.

In 1982, the Food and Drug Administration (FDA) approved human insulin as the first recombinant DNA product for clinical use in humans. Scientists at Genentech, Inc. (South San Francisco, CA) devised recombinant DNA methods for producing insulin in bacteria from synthetic insulin genes, and assembling the protein chains into biologically active insulin. Eli Lilly and Company (Indianapolis, IN) subsequently developed and marketed the recombinant DNA version of human insulin, under the trade name Humulin®, as a therapy for diabetes. Since that time, six additional human therapeutic agents produced using biotechnology have been approved for marketing in the United States (table 9-1):

- two recombinant DNA-derived versions of human growth hormone for long-term treatment of children with growth failure due to lack of adequate endogenous growth hormone,
- two recombinant DNA-derived versions of human alpha-2 interferon for treatment of hairy-cell leukemia,
- a recombinant DNA-derived human tissue plasminogen activator protein for treatment of coronary artery blood clots that trigger heart attacks, and
- a mouse monoclonal antibody preparation for preventing acute rejection in kidney transplantation.

These biotechnology products underwent separate testing and clinical trials to receive market approval from the FDA, even though several are

Table 9-1.—Biotechnology-Based Human Therapeutics With FDA Market Approval

Trade Name/Generic Name	Use	Company Receiving Market Approval
Humulin®/Human Insulin	Treatment of diabetes	Eli Lilly and Company
Protropin®[a]/Human Growth Hormone	Treatment of children with inadequate secretion of growth hormone	Genentech, Inc.
Humatrope®/Human Growth Hormone	Treatment of children with inadequate secretion of growth hormone	Eli Lilly and Company
Intron A®/Alpha Interferon	Treatment of hairy-cell leukemia	Schering-Plough Corporation
Roferon-A®/Alpha Interferon	Treatment of hairy-cell leukemia	Hoffman-La Roche, Inc.
Orthoclone OKT*3®/Monoclonal antibody against T-cells	Treatment for reversal of acute kidney transplant rejection	Ortho Pharmaceutical Corporation
Activase®/Tissue Plasminogen Activator	Treatment of cardiac arrhythmia	Genentech, Inc.

[a] First recombinant DNA product to be developed, manufactured, and marketed by a dedicated biotechnology company.

SOURCE: Office of Technology Assessment, 1988.

the same type of protein marketed by different companies for the same therapeutic use.

This chapter assesses the current U.S. investment in biotechnology as it applies to the discovery and development of human therapeutics. The following questions are addressed:

- How is biotechnology being used to discover new or better therapeutic pharmaceuticals?
- What basic and applied research programs related to pharmaceutical biotechnology are being invested in by the public and private sectors?
- How are factors such as gaps in basic and applied research, availability of funds, regulation, intellectual property protection, information access, and availability of trained personnel affecting overall investment in the development of human therapeutics derived from biotechnology?

APPLICATIONS OF BIOTECHNOLOGY TO HUMAN THERAPEUTICS

Biotechnology has become an integral component of many aspects of pharmaceutical research, easing the technical bottlenecks that slow the pace of new human therapeutic discoveries. Biotechnology has brought about significant innovations in methods for isolating and producing human proteins with therapeutic potential in human beings. The following sections summarize the state of the art of research in the development of human therapeutics made using biotechnology.

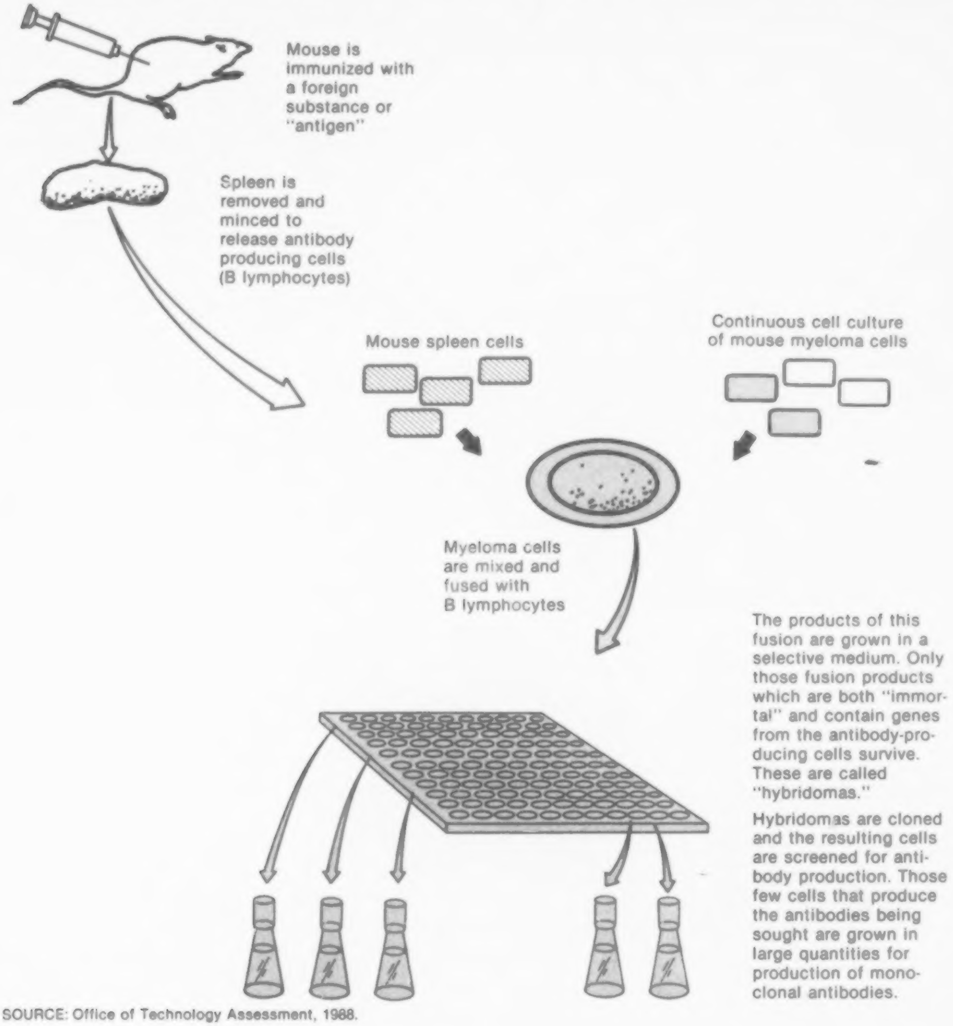
Biotechnology and the Development of Human Therapeutics

Scientific advances in biochemistry, cell biology, immunology, virology, structural biology, and related disciplines over the last 10 to 15 years have yielded an explosion in understanding about the structure and function of infectious agents and the machinery of cells at the molecular level. This substantial progress has been greatly enhanced by the development of methods for DNA and protein sequencing, DNA and protein synthesis, monoclonal antibody production from hybridomas (figure 9-1), recombinant DNA construction, and protein structure determination. Thus, compared to traditional approaches to drug development, biotechnology potentially offers a more rational or targeted strategy that involves an in depth understanding of the complexities of human biology (18,24).

The number of potential human therapeutics is increasing in two general categories because of advances in biotechnology:

- monoclonal antibodies made from mouse or human hybridoma cell lines; and
- human proteins produced from direct or engineered copies (clones) of genes.

Figure 9-1.—Preparation of Mouse Hybridomas and Monoclonal Antibodies


Mouse is immunized with a foreign substance or "antigen"
Spleen is removed and minced to release antibody producing cells (B lymphocytes)
Mouse spleen cells
Continuous cell culture of mouse myeloma cells
Myeloma cells are mixed and fused with B lymphocytes
The products of this fusion are grown in a selective medium. Only those fusion products which are both "immortal" and contain genes from the antibody-producing cells survive. These are called "hybridomas."
Hybridomas are cloned and the resulting cells are screened for antibody production. Those few cells that produce the antibodies being sought are grown in large quantities for production of monoclonal antibodies.

SOURCE: Office of Technology Assessment, 1988.

Monoclonal Antibody Products of Hybridomas

ORTHOCLONE OKT3® is a monoclonal antibody that targets a subset of the body's white blood cells (T-cells) responsible for acute rejection of transplanted tissue. This therapeutic, manufactured by Ortho Pharmaceutical Corporation (Raritan, NJ), is used to prevent acute kidney rejection. Whereas traditional drugs suppress the entire immune system, resulting in life-threatening infections, the value of OKT3® lies in its specificity for T-cells. At least three biotechnology companies (Centocor (Malvern, PA), Cetus Corporation (Emeryville, CA), and Xoma Corporation (Berkeley, CA)) are developing either mouse or human monoclonal antibodies against the gram-

Photo credit: University of California, San Francisco

Molecular biologist preparing for DNA cloning and in vitro mutagenesis experiments.

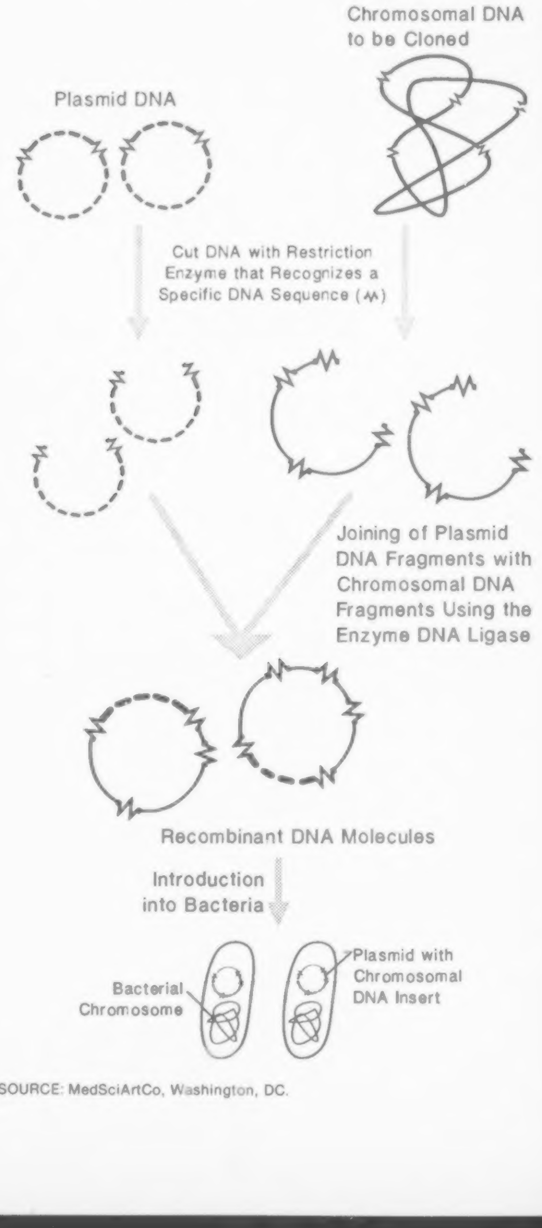
negative bacterial endotoxins that cause septic shock, a life-threatening condition characterized by a severe drop in blood pressure. Other therapeutic monoclonal antibodies under commercial development include those for reducing risks associated with bone marrow transplants, correcting for drug overdoses, and treating various cancers either directly or as targeted carriers of cytotoxic drugs (1,48).

There is also incentive to develop human myeloma cell lines for making human hybridomas. After repeated or long exposures to therapeutic antibodies from rodent sources, humans can become sensitive to the mouse antibodies and respond by making their own antibodies against them (8,26, 34,44). In addition, cell lines derived from mice often release pathogenic viruses that could pose dangers to humans if not removed from the monoclonal antibodies during their purification from mouse ascites fluid (57). An alternative method for producing monoclonal antibodies is to synthesize them from cloned genes in bacteria, yeast, or myeloma cells. Monoclonal antibodies with dual specificities, pre-determined specificities, and additional activities are all possibilities with recombinant DNA technology (69).

Products of Cloned Genes

With the exception of the one monoclonal antibody, all of the biotechnology-derived human therapeutics presently on the market and most of those in clinical trials are products of genes cloned by recombinant DNA technology (figure 9-2). Brief

Figure 9-2.—DNA Cloning Technology


Chromosomal DNA to be Cloned
Plasmid DNA
Cut DNA with Restriction Enzyme that Recognizes a Specific DNA Sequence (ʌʌ)
Joining of Plasmid DNA Fragments with Chromosomal DNA Fragments Using the Enzyme DNA Ligase
Recombinant DNA Molecules
Introduction into Bacteria
Bacterial Chromosome
Plasmid with Chromosomal DNA Insert

SOURCE: MedSciArtCo, Washington, DC.

Box 9-A.—Known or Expected Therapeutic Applications of Some Human Gene Products Under Commercial Development

Atrial Natiuretic Factor (ANF). One of the peptide hormones secreted by the heart; acts to regulate blood pressure, blood volume, and water and salt excretion; possible applications in treatment of hypertension and other blood pressure diseases and for some kidney diseases affecting excretion of salts and water.

Epidermal Growth Factor (EGF). A protein growth factor that causes replication of epidermal cells (those cells on the outermost layer of tissues); expected to have applications in wound healing (including burns) and cataract surgery.

Erythropoietin (EPO). A protein hormone growth factor normally produced by the kidney; causes the production of red blood cells; anticipated treatment for anemia resulting from chronic kidney disease; some potential for curing anemias associated with AIDS and other chronic diseases.

Factor VIII:C. A protein involved in blood clot formation; major application in prevention of bleeding in hemophiliacs (deficient in factor VIII) after injury.

Fibroblast Growth Factor (FGF). A protein that stimulates growth of blood vessels; may be useful in wound healing and treating burns.

Granulocyte Colony Stimulating Factor (G-CSF). One of a larger class of colony stimulating factors that stimulates production of the class of white blood cells called granulocytes; could be useful in treating leukemia and AIDS, possibly in concert with other chemotherapeutics.

Human Growth Hormone (hGH). A peptide hormone naturally occurring in the pituitary gland; used as a treatment for childhood dwarfism; expected to have broader therapeutics potential in wound healing or treatment of Turner's syndrome and small stature.

alpha-Interferon (a-INF). A lymphokine protein used as a treatment for hairy cell leukemia; possible broader applications in treatment of venereal warts, Kaposi's sarcoma (associated with AIDS), lymphoma, bladder cancer, and malignant melanoma.

gamma-Interferon (g-INF). A lymphokine protein that activates macrophage cells and interferes with viral replication; potential treatments for various cancers, AIDS.

Interleukin-2 (IL-2). A lymphokine protein hormone that causes immune system responses; potential treatment for various cancers.

Interleukin-3 (IL-3). A blood protein colony stimulating factor that promotes both red and white blood cell production at the earliest stages of cell development; potential applications in treatment of white blood cell deficiency in AIDS patients or that induced by radiation and chemotherapy exposures in other cancer patients.

Macrophage Colony Stimulating Factor (M-CSF). A colony stimulating factor that acts only on white blood cells of the monocyte/macrophage type; potential applications are expected for treatment of infectious diseases, primarily parasitic, but some bacterial and viral diseases; possible cancer therapy.

Superoxide Dismutase (SOD). An enzyme that seeks out superoxide free radicals in the blood and prevents damage when oxygen-rich blood enters oxygen-deprived tissues; applications in cardiac treatment and organ transplants.

Tumor Necrosis Factor (TNF). A protein growth factor with possible broad applications in antitumor and antiviral therapy.

Tissue Plasminogen Activator (TPA). A blood protein that activates plasminogen, a naturally-occurring blood protein that breaks down fibrin blood clots; used for dissolving the coronary artery blood clots associated with myocardial infarctions, or heart attacks, with other possible blood clot dissolving applications.

SOURCE: Office of Technology Assessment, 1988.

descriptions of the major recombinant DNA-derived proteins currently under commercial development for use as human therapeutics are given in box 9-A. Two other OTA reports describe the categories of proteins being developed as human therapeutics (e.g., regulatory proteins including the interferons and lymphokines; blood products; growth factors; and monoclonal antibodies) and the technologies used to make them (51,54).

Recombinant DNA methods can also be used to substitute, delete, or add nucleotides to the DNA that makes up a gene. Such alterations in the DNA lead to changes in the amino acids that make up its protein product. These biotechnologies for **protein engineering** have already been used commercially to facilitate protein purification processes, and they show promise for developing the second generation of human therapeutics from biotechnology (see box 9-B).

Biotechnology and the Production of Human Therapeutics

Scale-up and manufacturing technologies for the production of human therapeutics from cells containing recombinant DNA, or from hybridomas, are considered in detail in an earlier OTA report (51) and more recently in other reviews (7,28, 29,70). This section focuses, therefore, on the cells or organisms currently being used for the production of gene products and on some of the tech-

Box 9-B.—Protein Engineering and the Development of Human Therapeutics

The ability to make proteins function more efficiently, to operate under stressful conditions within the human body (e.g., the strongly acidic environment of the stomach), or to create totally new proteins that do not exist in nature are all possibilities of importance to the commercial development of novel human therapeutics. The drugmaker's wish list for "engineered" proteins includes those with enhanced therapeutic effects, those specific for particular disease agents, such as viruses, and those that are stable in the varied biochemical environments of the human body.

Recent advances in recombinant DNA procedures, the chemical synthesis of genes or gene fragments, protein structure determination, and computerized molecular modeling have brought about a new era of *protein engineering*. Protein engineering can be achieved either through direct modification of the amino acid molecules that comprise proteins, or by altering the DNA molecules of the genes that produce the proteins. The newer methods for modifying proteins at the DNA level are collectively referred to as *in vitro mutagenesis*, and they have brought new life to the field of protein engineering.

Protein engineering usually involves the substitution of one amino acid for another within a protein. Such procedures can be applied to the development of human therapeutic proteins, either to make more effective therapeutics, or to simplify the process used in their purification. Scientists at Cetus, for example, used in vitro mutagenesis to make amino acid substitutions in b-interferon and interleukin-2, both in advanced stages of clinical trials, to facilitate the process by which these proteins are purified from bacteria. The modification of proteins, by mutagenizing the genes that produce them, has also proved to be a useful tool for testing theories on the relationships between protein structure and function.

Advances in recombinant DNA technology also have made it possible to construct new proteins by substituting or deleting whole portions of genes. A gene made by combining portions of the genes encoding the receptor proteins for two potentially important human therapeutics—interleukin-2 and epidermal growth factor—was constructed in an effort to better understand the biological mechanism by which these growth factors function.

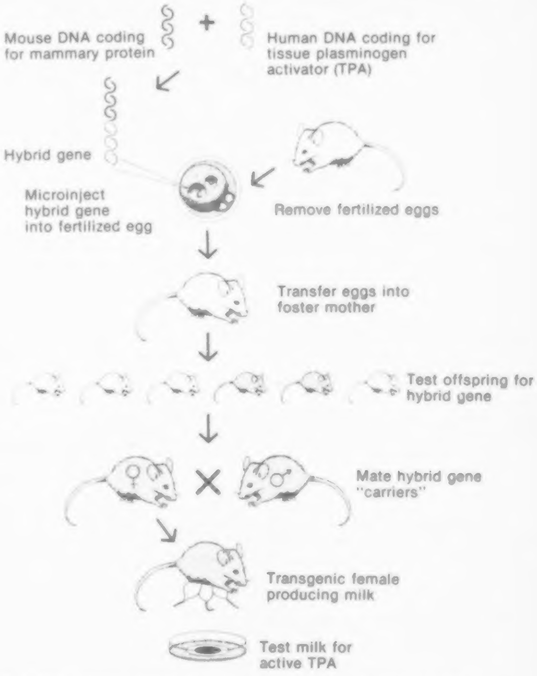
SOURCES: O. Bernard, B. de St. Groth, M.J.E. Sternberg, et al., "Knowledge-Based Prediction of Protein Structures and the Design of Novel Molecules," *Nature* 326:347-352, 1987. A.S. Moffat, "Protein Engineering," *Mosaic* 18:2-13, 1987. M. Ostrach, Cetus Corp., South San Francisco, CA, personal communication, December, 1987. V. Rath, and R. Fletterick, "Protein Structure and Design 1987," *Cell* 49:583-586, 1987.

nical limitations associated with the use of each source.

Once a human gene is isolated, recombinant DNA methods can be used to make it function in many foreign hosts, ranging from bacteria and yeast cells to insects, mice, and sheep. For human therapeutics made from recombinant DNA technology, vectors (plasmid or phage chromosomes designed to carry extra genes) have been constructed that maximize the expression of the gene product (the protein) in different cell types or organisms. Once synthesized, the cell may need to modify the human protein for proper functioning. These modifications can include the attachment of sugar molecules, by a process called glycosylation, or the removal of some terminal amino acids (45). Therefore, it is necessary to determine the appropriate organism or cell type from which large quantities of a human gene product can be easily purified in a form sufficiently similar to the protein as it is found naturally in human beings.

The choice of host cell or organism for the production of human therapeutics is decided mostly by logistic and economic factors (28), and in many cases, by the particular post-synthesis modification requirements of the protein (29,61). Recombinant DNA-derived insulin, alpha interferon, and human growth hormone—three marketed human therapeutics—are all produced in bacteria. Despite these successes, bacteria are not always able to synthesize human proteins that are similar enough to their natural human counterparts to function adequately. Human proteins that require special chemical modifications, like the glycosylated hormone erythropoietin, are best made in mammalian cell culture where they acquire optimal levels of glycosylation (63). On the other hand, the type of protein glycosylation varies among species and in higher organisms, and also varies from tissue to tissue. In those instances, it may be more economical to synthesize proteins in yeast with partially correct chemical modifications, and then modify the product in vitro (outside of the cell) (28). One alternative to mammalian culture for those proteins that require special modifications is production from the lactating mammary glands of an animal. Isolated genes can be injected into animal embryos (e.g., mouse, goat, sheep, cattle) and incorporated into the germ line where they can function just as the mouse's own genes (figure 9-3) (21). The latter technology is examined in a forthcoming OTA special report on *Patenting Life*. **The challenge for bioprocess engineers working with human proteins isolated from nonhuman organisms has been to devise methods for retaining protein activity while maximizing yields.**

Figure 9-3.—Mouse/Human Hybrid Gene Enables Mice to Secrete Human Therapeutic Proteins


Mouse DNA coding for mammary protein
+
Human DNA coding for tissue plasminogen activator (TPA)
Hybrid gene
Microinject hybrid gene into fertilized egg
Remove fertilized eggs
Transfer eggs into foster mother
Test offspring for hybrid gene
Mate hybrid gene "carriers"
Transgenic female producing milk
Test milk for active TPA

SOURCE: Adapted from Integrated Genetics, Inc., Cambridge, MA.

FACTORS INFLUENCING INNOVATION AND COMMERCIALIZATION

OTA identified six major factors that influence the rate at which biotechnology research will be transformed into commercial products in the area of human therapeutics. These factors, some of which might be considered incentives and others obstacles to product development using biotechnology, were identified in interviews with representatives of established pharmaceutical companies and dedicated biotechnology companies (DBCs), Federal agencies, and from a 1987 OTA workshop on "Factors Affecting Commercialization and Innovation in the Biotechnology Industry" (52). They are:

- gaps in basic and applied research;
- availability of R&D funds;
- regulation of products made using biotechnology;
- protection of intellectual property;
- access to information generated in biomedical research; and
- availability of trained personnel.

The availability of funds for *basic research* is the factor of central concern to those involved in developing new human therapeutic products. Nevertheless, each of these elements factor into the R&D process, and taken together, they influence the overall level of investment (including monetary, personnel, and other types of resources) in applications of biotechnology by the pharmaceutical business sector.

Gaps in Basic and Applied Research

Despite significant advances in recombinant DNA technology and the development of efficient protein production systems, major bottlenecks, or gaps in knowledge, remain in research ultimately applicable to the development of new human therapeutic agents. This section focuses primarily on the major research needs in the identification, isolation, engineering or chemical synthesis of new drugs, including new approaches for:

- isolating human proteins and genes;
- establishing relationships between protein structure and function;
- determining how proteins fold into active three-dimensional structures;
- developing animal models useful for elucidating the physiological roles of previously uncharacterized proteins;
- understanding mechanisms of protein maturation and export from cells; and
- administering protein drugs.

Isolating Human Proteins and Genes

There are probably over 50,000 proteins in the human body (11). **Only a few hundred of the human genes that produce these proteins have been isolated, however, so many more human genes will be needed before the full impact of recombinant DNA on the discovery of potential human therapeutic proteins is realized.** Currently, most scientists target specific genes and gene products for study, often using information from small amounts of the natural human protein to isolate the corresponding gene (53). A National Research Council panel urged that additional resources be given to scientists for developing the DNA mapping technologies necessary for identifying and isolating the entire set of human genes (40).

Establishing Relationships Between Protein Structure and Function

Regardless of the method used to isolate a human gene, the function of the corresponding protein product is rarely obvious from the structure of the gene. Studies aimed at determining the potential of human proteins as therapeutic agents depend on knowing how the proteins function in the human body. In the absence of experimental evidence for the function of a particular protein, scientists often attempt to predict the protein's function from its structure. From the DNA sequence of a gene, the genetic code can be used to predict the amino acid sequence of the corresponding protein. The next step is to predict from the amino acid sequence the three-dimensional structure of the protein. The final step, the prediction of a protein's function, is less straightforward. At the molecular level, **the "structure-function problem" refers to the difficulty scientists have in determining the relationship**

between the presence of a particular stretch of amino acids in a protein, and the activity or function of those amino acids (38).

A standard approach of biologists to the structure-function problem is to compare the structure of a protein with unknown function to a protein or proteins with known functions (figure 9-4). If structural similarities exist, then experimentally testable predictions can be made on possible functions of the uncharacterized protein. Computer methods for identifying amino acid sequence similarities among proteins, or DNA sequence similarities among genes, are available (16), as are methods for three-dimensional structure prediction and comparison (5). These tools need to be further developed for predictions of protein structure and function from sequence data to become more practical. In addition, in vitro mutagenesis techniques for engineering genes to produce modified proteins (protein engineering—see box 9-B) have advanced, but are still in need of further development (30). These techniques are important for making detailed molecular models of how specific protein structures correlate with particular functions.

Understanding How Proteins Fold Into Active Three-Dimensional Structures

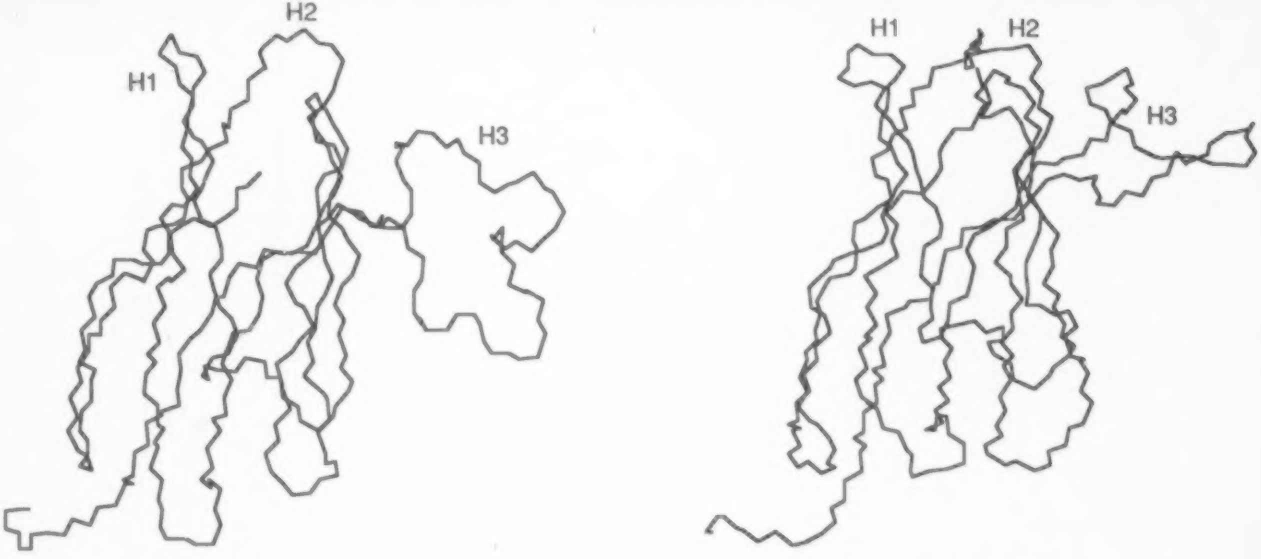
"Protein-folding is the genetic code expressed in three dimensions" (19). How does the linear sequence of amino acids in a protein code for its structure? How does the three-dimensional conformation of a protein drive its function? Sometimes the amino acid sequence of a protein with an unknown function is similar to that of a protein with a known function; in many such cases, the similarity is a valid indicator of comparable jobs. In other cases, the three-dimensional structure of a protein (the amino acid sequence folded into the actual structure of the protein) gives more reliable clues about function. At present, scientists cannot predict with certainty how the linear sequence of amino acids in a protein will fold into the protein's three-dimensional structure—thus the protein-folding problem. As more DNA sequences of genes are obtained, the problem will take on even greater significance. In a recent report, the National Academy of Sciences stated that protein folding is "the most fundamental problem at the chemistry-biology interface, and its solution has the highest long-range priority" (38).

The protein products of cloned human genes can be produced in and purified from other organisms or cells, but in the process, they often become improperly folded, inactive molecules. The human factor VIII blood clotting protein required by hemophiliacs (see box 9-A), for example, has posed significant problems for protein chemists trying to purify the recombinant DNA version from non-human sources (32). Because of such problems, it is important to develop a better understanding of how the chemical and physical properties of a protein guide it to become a properly folded, active structure under normal physiological conditions.

Most predictions of three-dimensional structure are based on theories of the behavior of amino acids in certain chemical and physical environments and on information gleaned from viewing the atomic structures of proteins through x-ray diffraction (5). X-ray diffraction of protein crystals is an important tool in the field of structural biology—the study of protein and other macromolecular structures. It is the most important technique for determining the three-dimensional structures of large proteins at the atomic level. Advances in x-ray crystallographic (15,65) and other biophysical technologies are needed so that more protein structures can be determined to give a solid foundation for further development of protein-folding theories.

Experimental evidence suggests that certain structural domains serve similar functions in a number of different proteins. Thus, it is the combination of domains that gives a protein its unique overall function (figure 9-4). Protein structure predictions have recently been used to propose a possible structure for Interleukin-2 in an important step toward understanding the interaction of this protein with its receptor during the immune response in humans (13). Once the protein-folding problem is solved, and methods for correlating structure with function are further developed, the road going from the DNA sequence of a gene to the function of its protein product will be considerably shortened, and in some cases, will pave the way for the development of promising new human therapeutic products.

Figure 9-4.—Structural Similarities Between the Domains of Different Proteins



CD4 domain 3

IgG variable heavy domain

Hn = hypervariable loops

```
                 (a)                      (b)      (H1)       (c)                   (c')      (H2)   (c")               (d)
IgG         | EVQLVQSG | GGVVQPGRSL | RLSCSSS | GFIFSS | YAMYWVRQA | PGK | GLEWVAIIW | DDGS | DQHY | ADSVKGR | FTISR | NDSKN |
CD4         |   QGKKVV |   LGKKGDTV | ELTCTAS |   QKKS | IQFHWKNSN | QIK |    ILGNQG | SFL  | TKGP | SKLNDRA | DSRRS | LWDQG |
            |          |            |         |        |           |     |           |      |      |         |       |       |
identities  |  Q  -    |  + - G-&+  | -L&C&&S |      S | + + W -   |   K |   ++&     |      |  -   | &-  -   | &     |     - |
                         ========================
                                  Seq.1

                (e)                   (f)                  (H3)                      (g)
IgG         | TLFLQMD | SLRPEDT | GVYFCAR |      DGGHGFCSSASCFGPD       | YWGQGTPVTV | SSAS |
CD4         | NFPLIIK | NLKIEDS | DTYICEV | EDQKEEVQLLVFGLTANSDTHL | LQGQSLTLTL | ESPP |
            |         |         |         |                         |            |      |
identities  |  + L +- | L- ED&  |   Y+C   |   -     +     &     &D   | + GQ& &+T+ | S&&  |
             ==============================                           ====================
                          Seq.2                                              Seq.3
```

identities	
Seq.1	75 %
Seq.2	57 %
Seq.3	79 %

An illustration of the three-dimensional structure of the CD4 receptor domain 3; CD4 is the membrane protein that is the cellular binding site for one of the proteins of the AIDS virus. The three-dimensional, computer-generated model for CD4 domain 3 was constructed by comparison with a known antibody structure (IgG). At bottom are shown the amino acid sequence comparisons between the two protein domains, illustrating the fact that proteins can be structurally similar even though they have few amino acid sequences that match directly.

SOURCE: Ernest Feutmans and Robert Fletterick, University of California, San Francisco, CA.

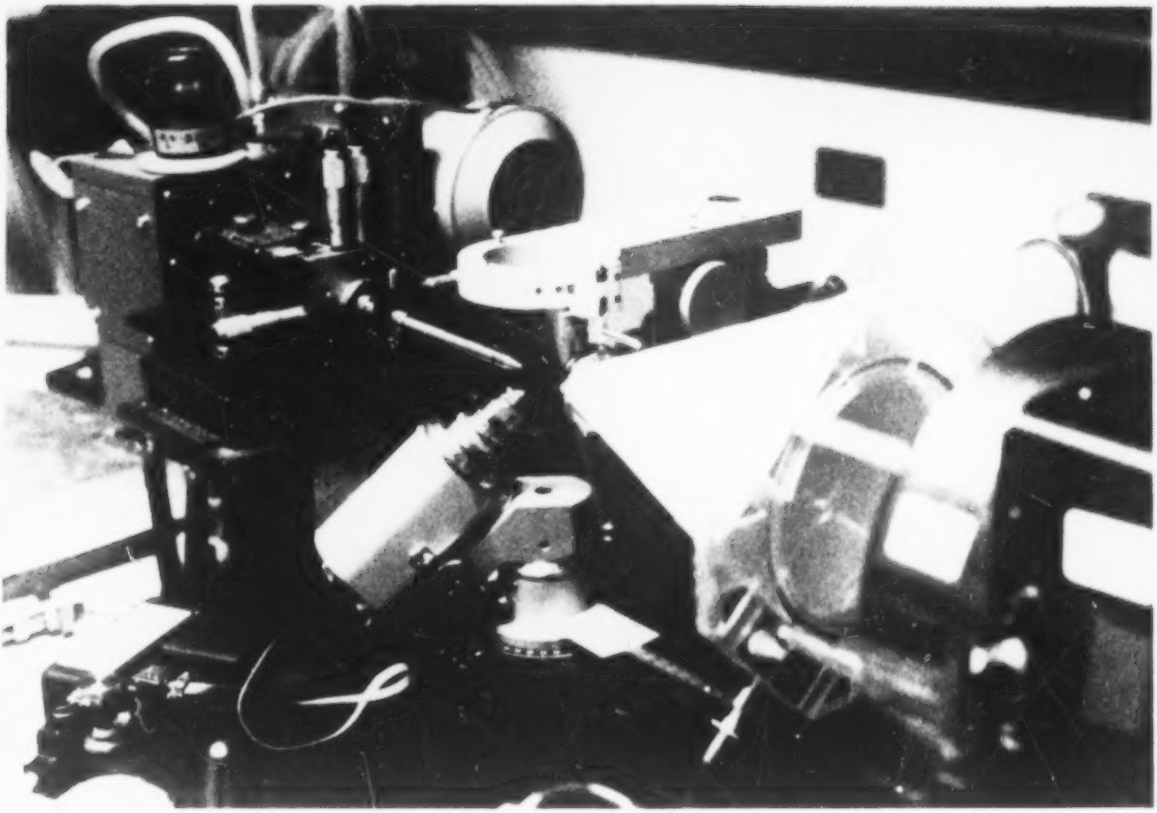


Photo credit: University of Texas Health Sciences Center, Dallas

Instrument for x-ray diffraction analysis of protein crystals used in three-dimensional structure determinations.

Developing Animal Models for Studying the Function of Human Proteins

The therapeutic potential of any newly isolated human protein can only be ascertained once its function in the body is known. With current technology, it is faster to clone a human gene than to establish the function of its protein product. As already described, there are theory-based tools for extracting functional information about a protein from both its amino acid sequence and its three-dimensional structure. The most direct method is to experimentally determine the role of a particular human protein under the physiological conditions of the human body. However, experimentation with untested protein products on humans is necessarily prohibited to protect human subjects. In animals, advances in recombinant DNA technology have made it possible to introduce human genes into germ lines shortly after the egg is fertilized (41). An example of such a transgenic animal is the mouse whose milk produces tissue plasminogen activator protein (21) (see figure 9-3). For transgenic animals to be useful in the analysis of human genes whose functions are not known, methods must be devised for directing genes to specific sites in the genome, and for assaying the physiological effects of introducing human genes into animals (53).

Understanding Mechanisms of Protein Maturation and Export From Cells

For many proteins, mammalian cell culture can produce a human protein with greater similarity to proteins isolated from natural human plasma or tissue than can bacteria or yeast cells. There are many problems, however, with the use of large-scale mammalian cell culturing for the production of human therapeutics, including: high costs; technical difficulties; infection of cultures with viruses and other agents that might be dangerous to humans; and contamination of products with proteins secreted from the host cells or with proteins present in the culture medium that may cause an immune response or be otherwise toxic to humans (7,9). The levels and types of contaminants in the final preparation of a human therapeutic is a major concern of both producers and Federal regulators, and a great deal of effort needs to be directed at finding technical solutions to these problems. In addition, since bacteria and yeast have proven to be commercially valuable systems for the production of human proteins from recombinant DNA, it is important to continue developing an understanding of the process of protein maturation (e.g., how and why certain chemical modifications occur) and export from these cells, so that better production methods might be devised.

Methods for Administering Protein Drugs

One of the greatest challenges to the development of proteins for use as human therapeutics is the requirement of special delivery mechanisms for proteins—both those derived from recombinant DNA and those extracted from human tissue and blood. Protein drugs are often ineffective if ingested, because they are rapidly broken down by enzymes in the gastrointestinal tract. When they do survive in such harsh environments, the large sizes of proteins can inhibit their absorption through the intestinal wall. Consequently, protein drugs are usually administered by subcutaneous, intramuscular, or intravenous injections, but even these delivery routes are associated with problems. Dosage is also a problem unique to protein therapeutics; many proteins, particularly hormones, must be released continuously at a controlled rate over a period of weeks or even months (25). In addition, prolonged exposure to incompletely processed human proteins can induce allergic responses.

Manufacturers of biological therapeutics are beginning to address these problems with a variety of innovative approaches. Protein engineering, for example, could potentially be used as a tool for more effective drug delivery. Industrial researchers used recombinant DNA and computer graphics-assisted molecular modeling to engineer a version of insulin that, when injected daily, is reported to behave more like the body's own insulin than do earlier versions of recombinant DNA-derived human insulin (49). While intravenous and subcutaneous delivery have been standard procedures for many years, methods for administering protein drugs through mucosal routes are now being developed. California Biotechnology, Inc. is developing Nazdel®, a nasal delivery system, as an alternative to insulin injections. Other protein therapeutics such as human growth hormone and a hormone secreted by the heart (atrial natiuretic factor, or Auriculin®), are also under study for intranasal delivery (2).

Photo credit: University of California, San Francisco

Scientist illustrating the use of computer modeling in protein engineering.

Research and Development Funding

Biomedical research encompasses a large number of disciplines, including biochemistry, virology, immunology, genetics, neurobiology, and cell biology. Research in these fields serves as the foundation for innovation in the pharmaceutical industry. The tools of biotechnology are now so intimately woven into each of these fields that it is difficult to differentiate between funding dedicated to biotechnology-based research and that going to more traditional technology. **The National Institutes of Health (NIH), the National Science Foundation (NSF), the Department of Defense (DoD), and the Department of Energy (DOE) are the government agencies funding the greatest amount of biomedical research that underlies applications of biotechnology to the development of human therapeutic products.**

The contributions of Federal agencies, the States, and U.S. industry to biotechnology research are covered in detail in chapters 3, 4, and 5, respectively. In this section, examples of notable biotechnology projects funded by Federal agencies supporting the greatest portion of biomedical research are identified. Investment by industry and philanthropic organizations in biotechnology research with implications for the development of new drugs is also discussed.

Federal Agencies

The National Institutes of Health (NIH). With the exception of the National Institute of General Medical Sciences (NIGMS), each institute of the NIH has as its principal mission the support of research on a range of diseases. NIGMS supports research and training in the basic biomedical sciences fundamental to understanding health and disease. Its primary function is to support U.S. and international research projects that can serve as the basis for the more disease-specific research undertaken by the other, categorical NIH institutes. The NIH has two categories of biotechnology research: basic research directly related to or using the new techniques that comprise biotechnology; and a larger science base of free-ranging research underlying biotechnology. The more applied areas of research fall under the first category.

The NIH estimates that 38 percent of its $6 billion fiscal year 1987 budget was devoted to biotechnology research. The National Cancer Institute (NCI), the NIGMS, and the National Institute for Allergy and Infectious Diseases (NIAID), were the three lead institutes for biotechnology funding, spending $645, $356, and $297 million, respectively (see table 3-2). NIH funds a number of biotechnology research grants that are pertinent to drug discovery and development. Particularly relevant to the discovery of human therapeutics are relatively new programs aimed at developing therapies for Acquired Immunodeficiency Syndrome (AIDS), stimulating research in protein structure determination and other areas of structural biology, and developing techniques for mapping and sequencing genomes. These projects often fund multidisciplinary research teams.

Under its Small Business Innovation Research (SBIR) grants program (see ch. 3 for further discussion) in fiscal year 1986, NIH funded $44.5 million worth of research at small companies, with nearly 40 percent awarded to companies using biotechnology in their research. Research on delivery systems for protein drugs, production methods for human therapeutic proteins, and other applications of biotechnology is also being funded by NIH at dedicated biotechnology firms and pharmaceutical companies (see table 9-2).

The National Science Foundation (NSF). The funding of basic research grants in genetics, cell biology, and biochemistry is the major mechanism of NSF for supporting biotechnology research with long-term applications in human therapeutics. However, while NIH contributes the greatest share of basic research funds to independent investigators, other agencies, such as NSF, are making significant contributions to the discovery of novel pharmaceuticals by funding large multi-investigator projects in applied research. NSF funds an Engineering Research Center (ERC), called the Biotechnology Process Engineering Center, at the Massachusetts Institute of Technology (see box 3-A). The Center has programs in genetics and molecular biology, bioreactor design and operation, product purification, and biochemical process engineering systems.

Table 9-2.—Representative Biotechnology Small Business Innovation Research (SBIR) Program Grants Funded by the National Institute of General Medical Sciences in Fiscal Year 1987

Biotechnology Firm	Title of Research Grant
Radiation Monitoring Devices, Inc. Watertown, MA	Improved gel electrophoresis for medical research
Genelabs, Inc. San Carlos, CA	Rapid approaches for production of genomic DNA probes
Collaborative Research, Inc. Lexington, MA	Analysis of yeast glycosylation of a human glycoprotein
Biosym Technologies, Inc. Rockville, MD	Computer-assisted protein design
Biotech Research Laboratories, Inc. Rockville, MD	Porous microcarriers for growing cell cultures
Litron Laboratories, Ltd. Rochester, NY	Genetic Toxicology Testing by high-speed flow cytometry
Applied Sciences Consultants, Inc. San Jose, CA	Computer folding of RNA using Monte Carlo method
Biogen Research Corporation Cambridge, MA	Production of recombinant proteins in milk
TSRL, Inc. Ann Arbor, MI	Technology for oral delivery of first pass drugs
Genex Corporation Gaithersburg, MD	Bacillus hosts for pharmaceutical protein secretion
Electrocell Buffalo, NY	Electrofusion and electropermeation of cells
Verax Corporation Lebanon, NH	An improved system for mass culture of human hybridomas
Stratagene Cloning Systems San Diego, CA	New chromosomal jumping vectors for gene mapping

SOURCE: The National Institute of General Medical Sciences, 1988.

The NSF, the North Carolina Biotechnology Center, and several corporations jointly fund the Monoclonal Lymphocyte Technology Center. The Center supports research at several North Carolina universities in genetic engineering, lymphocyte biology, immunochemistry, and bioengineering as they apply to the production and use of monoclonal antibodies. The major goal of the programs supported by the Center is to stimulate university-industry cooperative research in areas with good potential for commercialization.

The Department of Energy (DOE). The Office of Health and Environmental Research (OHER) is the component of DOE with a mission in biomedical research. The primary mission of OHER is to study sources of radiation, pollution, and other environmental toxins (particularly those related to the generation of energy), to trace them through the environment, and to determine their effects on human health and the environment. DOE's commitment to funding a major initiative to map the DNA in the human genome (the entire set of human chromosomes) could be particularly relevant to the application of biotechnology in the pharmaceutical industry. This commitment stemmed from the work of the DOE national laboratories on developing technologies to isolate human chromosomes and examine their structure. An outside advisory panel to OHER recently proposed that DOE request $20 million in additional funds for fiscal year 1988, $40 million in fiscal year 1989, and $200 million in funds by fiscal year 1993 for mapping the human genome at both academic and National Laboratories (55). DOE spent $4.7 million on projects related to mapping genes on human chromosomes in fiscal year 1987, and received an appropriation of $11 million in fiscal year 1988 to expand their gene mapping efforts.

The Department of Defense (DoD). While biological research is not the main mission of DoD, some areas of biotechnology research are supported by its various components. Each military service, especially the Army and the Navy, conducts some research related to the health needs of military personnel or to defenses against chemical and biological warfare. Over $2 million per year is being spent by DoD through its Defense Advanced Research Projects Agency (DARPA) program on university research aimed at protein structure determination and solving the protein folding problem. Biotechnology R&D at the U.S. Army's Medical Research and Development Command Laboratories, such as the unclassified research at the Institute of Infectious Diseases (USAMRIID), has led to the development and testing of a number of internationally important vaccines. USAMRIID spent about $20 million in fiscal year 1987 for applied medical biotechnology research.

Joint Agency R&D Funding. Besides large contract research such as GenBank®—a DNA sequence database funded primarily by NIH and DOE—the joint funding of multi-investigator biomedical research programs by NIH, NSF, and other Federal agencies is uncommon. **Joint agency research funding might, in certain instances, be an appropriate mechanism for accelerating the ap-**

plication of biotechnology to neglected areas of biomedical research.

The States

The States have few programs directed solely at pharmaceutical biotechnology applications (see ch. 4). The Center for Advanced Research in Biotechnology (CARB) based in Shady Grove, MD is one State-supported biotechnology research program with emphasis on human therapeutic design. Protein engineering and rational drug design are the focus of CARB (see box 9-C). The North Carolina Biotechnology Center, funded in part by the State of North Carolina, is contributing approximately one-third of the funding for a new Engineering Research Center at Duke University that will use emerging technologies to develop treatments for cardiovascular disease.

Industry

Setting up the infrastructure and facilities for developing and manufacturing biotechnology-derived human therapeutics is expensive. Established corporations can support these initial costs from profit on sales revenues from traditional drugs, whereas dedicated biotechnology companies (DBCs), in general, continue to rely on capital from contract/collaborative research agreements with large companies, and private and public stock offerings.

Box 9-C.—Center for Advanced Research in Biotechnology (CARB): A Research Facility for Protein Engineering and Rational Drug Design

The University of Maryland, the National Bureau of Standards (NBS) and Montgomery County, MD have established a joint venture called the Center for Advanced Research in Biotechnology (CARB). The aim of this research organization is to make the State of Maryland a national leader in biotechnology by inspiring collaborative research among local academic, government, and industrial scientists.

CARB researchers are currently housed at NBS, but are expected to relocate by the end of 1988 to CARB's future headquarters at a 40,000-square-foot facility in Rockville, MD. The venture's founders hope that having CARB's research facility in close proximity to the National Institutes of Health, the Food and Drug Administration, the Department of Agriculture research headquarters, and a number of commercial biotechnology firms will greatly enhance its chances for success.

The Center has a singular biotechnology research goal that greatly complements the needs of the pharmaceutical industry: to use genetic engineering, computerized molecular modeling, and biophysical techniques to radically reduce the time and effort required to determine the atomic structure of proteins and to effectively model and predict their properties. It is expected that meeting this objective will help build the foundation for the emerging fields of protein engineering and rational drug design. Additional areas of related research include protein separations, biosensors, and biothermodynamics.

Officials at CARB are putting together a multidisciplinary team of scientists and engineers and providing them with state-of-the-art biotechnology instrumentation and facilities. From NBS, CARB hopes to derive expertise in physical and chemical measurement technologies that are relevant to macromolecular structure determination and analysis. University of Maryland scientists and a group of visiting academic and industrial scientists are also to be housed at the CARB facility. Training for graduate students and postdoctoral scientists is anticipated as well.

CARB is the furthest along of four proposed research centers established in the Maryland Biotechnology Institute by the University of Maryland Board of regents in 1984. CARB received a one-time allocation of $9.5 million from Montgomery County. The Maryland General Assembly appropriated approximately $1.4 million to CARB for fiscal year 1988 for personnel salaries and equipment. The NBS will also contribute $1.5 million to the Center's operating budget in fiscal year 1988.

SOURCES: CARB, Shady Grove, MD, promotional pamphlet, 1987. Walter Plosila, Montgomery County High Technology Council, Rockville, MD, personal communication, April 1988.

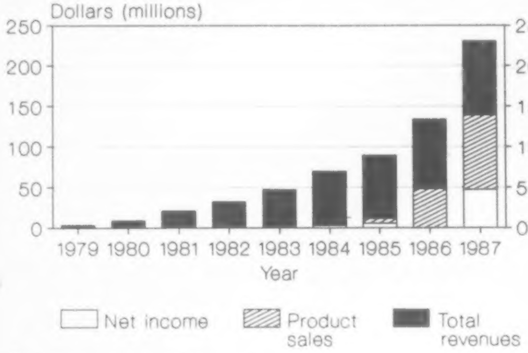
OTA surveyed 296 DBCs in Spring 1987; of these, 63 firms (21 percent) had a primary research focus in human therapeutics. The mean R&D budget of biotechnology companies dedicated to therapeutics was $9 million in 1986 (compared to a mean of $4 million for all DBCs), and a total R&D investment of $0.6 billion.

Fifty-three large, established corporations were surveyed in July 1987; of these, 14 corporations (26 percent) had a primary biotechnology research focus in human therapeutics. These pharmaceutical corporations had a mean biotechnology R&D budget of $16 million in 1986 (compared to $11 million for all established corporations), and a total biotechnology R&D investment of $0.2 billion, or 33 percent as much as the DBCs. The total R&D budget of the large corporations with a primary focus in human therapeutics was $3 billion in 1986, making biotechnology R&D only 7 percent of their total R&D expenditures.

More than for any other business sector, applications of biotechnology to the pharmaceutical industry are moving from the technology development phase to the clinical phase. Contributing to this transition, among other factors, is that between 1983 and 1986, the top management of many of the DBCs changed from the early scientist/entrepreneurs to professional managers, often from the larger, established corporations (33). Nevertheless, over the next several years, revenues from biotechnology product sales will be a reality for only a few firms specializing in human therapeutics. Profit from sales of more traditional pharmaceuticals (e.g., products of chemical synthesis) is still the primary source of biotechnology R&D funds for established companies, while even the most successful DBCs continue to rely on revenues from contract/collaborative arrangements and other outside sources (see ch. 5).

The long-term independence of the DBCs depends upon their ability to continue to raise the capital needed to become fully integrated pharmaceutical companies. A fully integrated company invents, develops, and markets products independently. In the view of most industry analysts, Genentech, Inc. is the only DBC, thus far, that has achieved the goal of becoming a fully integrated pharmaceutical company (figure 9-5). As discussed in chapter 5, the primary source of capital for companies striving for independent growth must change from venture capital, private or public equity investments, or contract research revenue, to revenues from product sales. Becoming a fully integrated pharmaceutical company is not the goal of each of the DBCs that specializes in human therapeutics, however, and it is an unlikely option for the majority.

Figure 9-5.–The Financial Maturation of a Dedicated Biotechnology Company



*Net income loss of $352.2 million.

SOURCE: Genentech, Inc., 1988.

Philanthropic Organizations

Biomedical research, including that involving biotechnology, enjoys the greatest level of private funding of all the sectors considered in this report. Endowments used to fund biomedical research are provided by numerous foundations, ranging from disease-specific foundations, such as the National Huntington's Disease Association and the Cystic Fibrosis Foundation, to very large organizations targeting research at diseases affecting large numbers of Americans, such as the American Cancer Society.

In the last several years, the Howard Hughes Medical Institute (HHMI), a medical research organization with an endowment of over $5 billion, has emerged as a major source of funds for researchers in a number of biomedical fields that involve biotechnology research. The Institute has increased its biomedical research funding dramatically over the last decade, from about $15 million in 1977 to over $168 million in 1987 (10).

HHMI operates three main research programs. The first and largest sponsors research in 27 laboratories in medical centers throughout the United States. Research funded by the Institute focuses on five main areas: genetics, neurobiology, cell biology, immunology and structural biology. The second major program includes the human genome program for international data collection and coordination of genome mapping projects, and the Cloister project, a joint effort with NIH to encourage medical students to pursue careers in medical research by enabling them to spend a year at NIH. The third program is the Institute's newest, and focuses on three main areas: graduate training fellowships; research resources grants; and undergraduate science education. Programs for promoting public understanding of science and for evaluating biomedical ethics issues are also being evaluated for this program. The Institute will dedicate at least $500 million to this third major program over the next 10 years (10).

Leaders of the HHMI professed a desire to address gaps in the NIH basic research program at a NIH Director's Advisory Committee meeting in June 1987 (43). The Institute's Director also expressed interest in working with NSF to ensure a strong national program of training grants for doctoral students in biomedical research disciplines (10). The influx of HHMI funds in biomedical research, much of which involves biotechnology, is an important supplement to government funding, but deficiencies in basic research funding could arise if such private investments are considered as substitutes rather than supplements to Federal funds.

Regulation of Pharmaceutical Biotechnology

For DBCs participating in the high value-added human therapeutics industry, the renewal of funds for R&D and ultimately the survival of those companies depends on the incentives and barriers along the path to market approval of their products. The regulatory component of the human therapeutic development process is perceived by both entrepreneurial and established companies as the major factor influencing the time required to develop a pharmaceutical product.

The debate over the rigorous and lengthy drug regulatory process has gone on for years. Arguments have been made that when too strict, regulation becomes prohibitive to pharmaceutical development. Overly stringent regulation could impede international competitiveness, and compromise human health by reducing the availability of therapeutic products. On the other hand, the private sector and the general public continue to stress the importance of protecting public health from unsafe or ineffective drugs. As a background for analyzing regulatory issues relevant to biotechnology products, this section describes the mechanisms currently employed in the United States for regulating human therapeutics. The Food and Drug Administration (FDA) is the regulatory agency with purview over the development of therapeutic products.

Biotechnology Regulatory Policy at FDA

An underlying policy question addressed by the White House Office of Science and Technology Policy (OSTP) in the Coordinated Framework for Regulation of Biotechnology was whether the regulatory mechanisms that pertained to products developed by traditional techniques were sufficient for regulating products produced using recombinant DNA and other new biotechnologies (51 F.R. 23310). Congress gave FDA authority, under the Federal Food, Drug and Cosmetics Act (FFDCA) and the Public Health Service Act (PHSA), to regulate products regardless of how they are manufactured. These laws authorize the FDA to monitor the testing of a new drug for safety and efficacy before it can be marketed for human use in the United States. The FDA has determined that there is no need for new administrative procedures and regulations specific for products made by biotechnology. In its final policy statement, **the FDA indicated that it would not classify products of recombinant DNA or hybridoma technologies any differently from those produced by traditional techniques, and that such products are already covered under existing statutory provisions and regulations for drugs and biologics for human use.**

The New Drug or Biologic Approval Process

The general process for obtaining new drug approval includes four main stages: preclinical (animal) studies; clinical investigation; application approval to market the new product; and postmarketing surveillance.

Investigators planning to conduct clinical investigations on human subjects with new products must file a Notice of Claimed Investigational Exemption (IND). The IND must contain information on drug composition, manufacturing data, data on experimental controls, results of animal testing, the training of investigators, intended procedures for obtaining the consent of subjects and protecting their rights, and an overall plan for human clinical studies. Detailed records of clinical investigations are required by the Center for Drug Evaluation and Research before a New Drug Application (NDA) for marketing approval will be considered. The Center for Biologic Evaluation and Research also requires such documentation for biologics (e.g., blood proteins). In addition, each biologic product lot must be characterized, and an establishment license for the production facilities must be obtained before a Product License Application (PLA) for marketing approval will be considered (56). Proteins with therapeutic potential fall under the purview of one or the other of the two Centers.

Special "Points to Consider" bulletins have been issued by FDA for products made using recombinant DNA and hybridoma processes. These include information to assist manufacturers in developing and submitting to FDA applications for approval of such biotechnology products for investigation or marketing. The FDA has requested assistance from product developers in the continuing development of the "Points to Consider" documents (53 F.R. 5468).

FDA Approval of Human Therapeutics From New Biotechnologies

Seven human therapeutics made using recombinant DNA or hybridoma technologies have thus far been approved for marketing by the FDA. **To date, the mean time spent by companies taking their biotechnology products through clinical trials and regulatory review at FDA (i.e., from the filing of an IND to the approval of an NDA or PLA) has been five years, significantly less than the 10- to 15-year average estimated for conventional drugs (67).**

For some of these therapeutics, clinical data on their counterparts, or on close analogues prepared from human plasma or tissues by non-biotechnological methods, were available. For example, substantial information already existed on the effectiveness of human growth hormone for dwarfism and on porcine insulin for diabetes—each prepared by conventional techniques (31). A key component of clinical trials for some of the seven biotechnology products now on the market was thus to demonstrate that the biotechnology products are as safe and effective as products prepared by conventional means.

The lack of previous preclinical or clinical studies on a potential protein drug has not, however, appeared to slow the regulatory approval process for biotechnology products at the FDA. Genentech, Inc.'s tissue plasminogen activator protein (Activase®) was approved for marketing only four years after the IND was filed, even though the manufacturing method was modified in the process (47), and there were no prior clinical studies with the protein (32). On the other hand, some biotechnology products, such as interleukin-2, have been in clinical trials for substantially longer times. Over the last several years, there has been considerable controversy surrounding the degree to which the effectiveness of this protein as an anti-cancer agent balances with its toxicity in human beings (1,35). Biotechnology products do not have a monopoly on the "fast-track" at FDA (3). For example, the NDA for azidothymidine (AZT), a non-protein drug that is not a product of biotechnology, was approved in March 1987 for treatment of AIDS symptoms, only 4 months after it was filed, and only two years after the IND was submitted (27). **Therefore, therapeutic products whose effectiveness can be demonstrated easily, and for which an efficient production method and dosage form can be readily determined, are likely to be approved in a timely manner, while others will require more extensive clinical studies.**

In addition to the seven biotechnology products already approved for marketing by the FDA, there are nearly 400 human therapeutics (produced either by cells that express cloned genes or by hybridomas) in some stage of clinical trials (32). Compared to the total number (25,000) of active INDs for all drugs and biologics currently on file at the FDA, the number of biotechnology products is small—representing only about 2 percent of potential therapeutics in some stage of human clinical trials (32). Nevertheless, in 1986 alone, 20 new human therapeutics were approved, of which four were products made using either recombinant DNA or hybridoma technologies. INDs for products made using the new biotechnologies are currently being filed in the Center for Biologic Evaluation and Research at a rate of about 125 per year, corresponding to nearly 50 percent of the total new INDs for 1987 (32). Meanwhile, the number of FDA personnel available to review the data from the relevant clinical studies has not increased proportionately (32, 71). The FDA Commissioner reported that these factors, combined with the recent emphasis at the FDA on speeding the review of applications involving drugs and biologics that are potential AIDS therapies, could cut into the Agency's resources for processing biotechnology product applications aimed at other therapeutic uses. Despite these concerns, **the relatively short time required to obtain market approval of human therapeutic products made using the new biotechnologies, and the high proportion of biotechnology products approved, should help sustain the current high level of public and private R&D funding for the application of biotechnology to human therapeutics in the near term.**

Recent Legislative Actions

Since the 1984 OTA report on commercial biotechnology (51), Congress acted in at least two areas involving drug regulation that influence the level of industrial investment in biotechnology-based human therapeutics: orphan drugs and drug exports.

The Orphan Drug Act.—Prior to 1983, pharmaceutical companies had little incentive to invest research funds and personnel in developing drugs likely to yield only limited financial profit. Small biotechnology companies developing innovative new techniques were even less likely to invest any of their limited R&D budgets in unprofitable human therapeutics. Drugs for such rare afflictions as Huntington's disease and Turner's Syndrome, that affect only a small population, were thus commonly known as "orphan drugs." In 1983, Congress amended the FFDCA with the "Orphan Drug Act" (Public Law 97-414) to provide incentives for developing drugs for rare diseases that would otherwise not be developed because the anticipated financial rewards were insufficient. A 50 percent tax credit for the cost of conducting clinical trials and 7-year market exclusivity were the key incentives provided in the Act. **The 7-year market exclusivity provision of the Act was designed to protect companies selling drugs that were ineligible for product or use patents, were off patent, or had little patent term outstanding.** Such companies could not otherwise be protected from competition from firms that were already marketing the drug for other therapeutic applications, and thus would not be able to recoup their costs in developing the product for an orphan application.

The Act has been amended twice. A 1984 amendment (Public Law 98-551) defines a rare disease or condition as that which affects fewer than 200,000 persons in the United States, or more than 200,000 persons for which it is clear that the cost of developing the drug will not be recovered by sales of the drug in the United States. **A 1985 amendment (Public Law 99-91) authorizes seven years of exclusive marketing approval for all orphan drugs regardless of their patentability, with the intention of encouraging private pharmaceutical companies to invest more in orphan drug development** (50). In addition, the amendment reauthorizes grants and contracts for clinical testing of orphan products, authorizes grants and contracts for preclinical testing, and establishes a National Commission on Orphan Diseases.

More than one company can receive the orphan designation for a particular use of a product, entitling them to the tax credit incentive for conducting clinical trials. However, in the cases where several sponsors seek marketing approval at the same time, only the first sponsor to receive approval is awarded the 7-year market exclusivity for that drug approved for that particular use. The approval of all others is delayed until the end of the 7-year period. The provisions of the Orphan Drug Act have stimulated new commitments to orphan drugs by both research-oriented pharmaceutical companies and DBCs (50,59). As of December 1987, a total of 179 drugs and biologics had been given an orphan designations for specific therapeutic uses (50). Of these, there were eight cases in which more than one company had initiated development of the same drug.

The awarding in 1985 and 1986 of 7-year market exclusivity rights to two companies for the use of their recombinant DNA-derived human growth hormones as a treatment for a rare form of childhood dwarfism has spurred substantial controversy (14,20,37,42). The second version of human growth hormone differed from the first by one terminal amino acid, and may cause less of an immune response in human beings. By approving the second product, the FDA indicated that they considered it a different, and presumably a more effective product, than the first. Other companies are also developing versions of recombinant DNA-derived human growth hormone, and view their own products as having therapeutic advantages as well (66). Analysts predict a potential annual market of over $150 million for human growth hormone, which is one likely reason for the competition among firms for exclusive marketing rights. **Human growth hormone is only one of several biotechnology products that have received "orphan" designation from the FDA that are expected to yield substantial revenues.** Other products include erythropoietin, epidermal growth factor and superoxide dismutase (see box 9-A). Each of these also show potential for additional, non-orphan therapeutic uses and greater long-term profitability.

Competition among U.S. companies for access to future market shares of a few of the same "orphan" biotechnology products is already evident, leading some observers to question whether a highly profitable drug, or one with broad potential applications outside the particular rare affliction warranting its orphan designation, should be eligible for special regulatory status (17,42,50). The market exclusivity provision in the Orphan Drug Act was not intended to be applied unless it is a necessary incentive for innovation. The Committee on Energy and Commerce in the U.S. House of Representatives reported their concern that there will be a sizeable number of drugs developed using the new biotechnologies that will be sponsored by more than one company. The primary reason, in the view of the Committee, is that these companies are not confident about the patentability of their products, and believe that the 7-year market exclusivity provision of the Act is an excellent alternative (50).

Drug Export Amendments Act of 1986.—Until 1986, the United States banned the *export for sale* of drugs and biologics not yet approved by the FDA. (Prior to the Act, unapproved drugs could be exported for investigational use only.) The FFDCA was amended in the 99th Congress to establish conditions for the commercial export of new drugs and new animal drugs and biologics manufactured but not yet approved for sale in the United States. The new provisions are referred to as the "Drug Export Amendments Act of 1986" (Public Law 99-660).

Commercial biotechnology trade groups were major advocates of this legislation, arguing that previous export restrictions on drugs and biologics not yet approved by the FDA put them at a competitive disadvantage by forcing them either to build plants abroad or to license their valuable technology to potential competitors. **The Drug Export Amendments Act allows, under certain conditions, U.S. pharmaceutical manufacturers to export for commercial purposes drugs and biologics to any of 21 developed countries provided that the drug or biologic has been approved for sale by the importing country** (21 U.S.C. Sec. 382(b)(1)). The exporting company must have an effective IND exemption allowing testing on human subjects, and be actively pursuing final product approval. If a listed country has not approved the product for sale, it may still receive the product for purposes of export to another country on the list in which the drug has been approved.

The Drug Export Amendments create a new export category for the sale of semi-processed,

or biological intermediate products (e.g., a strain containing a recombinant DNA molecule). Under the law, a partially processed biological product that will be used as a therapeutic can be exported for sale upon FDA approval. To obtain FDA approval, the exporter must show that the product is manufactured in compliance with Good Manufacturing Process regulations; the product is labeled appropriately; and there must be certification from the importing company that the finished product is approved or approval is being sought. The provision for partially processed biological products could be particularly important to entrepreneurial companies, such as the DBCs, with budgetary constraints that preclude them from building facilities abroad.

The new drug export laws might benefit DBCs seeking new markets more than large, established corporations using biotechnology. Many established pharmaceutical companies have licensing agreements with international affiliates, or with foreign companies to manufacture their products locally. In contrast, less established biotechnology companies do not want to license out all of their technologies to foreign competitors, but they cannot generally afford to build facilities in several countries. The new Drug Export Amendments lessen the likelihood that the DBCs will lose their share of a product in foreign markets—where the drug could be approved first—by the time FDA approves the drug for marketing in the United States.

Opponents of the new drug export legislation voiced concern that products not yet rigorously tested would be eligible for export. In their view, once an unapproved drug leaves the United States, the FDA will have great difficulty monitoring problems such as mislabeling or illicit shipment to other nations, especially those with little or no regulatory restrictions. It is still too early to establish whether these concerns have been substantiated by FDA actions.

Intellectual Property Protection

The legal protection of intellectual property is a necessary factor for encouraging investment. Reliable patent protection stimulates innovation and reduces the focus on developing analogs or modifications of drugs that have already been proven effective. **When intellectual property laws are unclear, the companies developing important new products, such as human therapeutics, are forced to invest valuable resources in expensive and time-consuming litigation.** In the case of human therapeutics made using recombinant DNA technology, the litigation has involved all types of patents, including those for the products themselves, the processes used to manufacture and purify them, and their various uses.

Broad Scope of Patent Claims

A widely held view of industrialists is that the scope of the patent claims for biotechnology-based human therapeutics is too broad (52). An example of litigation over broad patent claims is that involving the tissue plasminogen activator protein (TPA). A British court revoked a TPA patent that Genentech, Inc. had been awarded in the United Kingdom. The court ruled that the claims in the patent were too broad upon a challenge by the Wellcome Foundation (England) (22). Genentech, Inc.'s U.S. patent for TPA is still pending. Genetics Institute (Cambridge, MA) was awarded broad process patent coverage for a purification method for erythropoietin (EPO) from *any* source. This decision is being challenged by Amgen (Thousand Oaks, CA), which has product and process patents pending for EPO (1,22).

Effects of Infringement Suits on Wall Street

Infringement suits between companies producing human therapeutics by recombinant DNA technology have, at the very least, temporary effects on the investment community. On September 12, 1986, for example, Genentech, Inc.'s stock plunged 10.5 points based on the news that Hoffman-La Roche, Inc. (Nutley, NJ) had sued for infringement of their patent covering synthetic human growth hormone. Likewise, the issuance of Genetics Institute's patent on EPO sent Amgen stock down $6.75 per share from $38.25, and Genetics Institute's stock up $4.75 per share from $31.25 on the day of the announcement, July 1, 1987. This oscillating investment activity reflects, in part, the lack of case law histories for biotechnology patent infringements. **There is a long case law history for patents on traditional pharmaceuticals, but there is little information investors can use to determine the potential outcome of litigation over patents on human therapeutics derived from biotechnology.** The creation 4 years ago of the Court of Appeals of the Federal Circuit has resulted in a strong presumption of patent validity for all classes of patents (46).

What Is Patentable?

The U.S. Patent and Trademark Office has four main criteria for patentability of an invention: it must be novel, possess utility, be nonobvious, and the patent must enable others in the field to use the invention (64). Products of biotechnology are complex proteins that must maintain a certain three-dimensional structure, and in many cases acquire certain chemical modifications, in order to function at their full potential. Thus, depending on the organism used to produce the protein, and the process used to purify it, two recombinant DNA-derived versions with identical amino acid sequences could fold into three-dimensional structures with different levels of activity. This leads to questions on whether the patent on one protein product excludes the rights to patent all other versions. Another question regarding biotechnology patents relates to the nonobviousness criteria. Once a protein is discovered, is it obvious to produce it using recombinant DNA technology? For these and other reasons, some industry analysts believe that second and third generation recombinant DNA-based human therapeutics will be more easily protected under existing patent laws (1,22). Second generation protein products made using biotechnology can be those modified by protein engineering to have enhanced activity, or those made by a sufficiently different process than the first generation product. The patent protection of these products is uncertain, but the number of companies developing such products reflects high hopes (see ch. 5). There are at least five companies competing for second generation tissue plasminogen activator protein, for example.

Alternatives to Patent Protection

Pharmaceutical companies trying to protect their human therapeutic products may use patents, trade secrets, or copyrights. Recombinant DNA technology offers the pharmaceutical industry new methods for producing proteins that already exist in nature. As long as it does not naturally occur in pure form, and the purification process is not obvious, a therapeutic protein can be patented by the first individual or individuals to create a purified version. Recombinant DNA-derived insulin and human growth hormone were not patentable because purified forms had been prepared in the past using conventional techniques. However, the non-recombinant DNA-derived human alpha interferon was patented (46).

Although patents are the strongest protection and most favorable, there are certain circumstances under which trade secret protection could be preferable (see ch. 6). Process patent protection is not as broad and enforceable as product patent protection can be, so it is sometimes desirable to make innovative processes trade secrets. The advantages of trade secrets are that they do not have to be published, nor do they have to meet the patent requirements of novelty and nonobviousness (51).

Other Intellectual Property Issues

Another issue of intellectual property protection that can influence the level of investment in pharmaceutical applications of biotechnology is the infringement of U.S. process patents by developing and newly industrialized countries. Emerging biotechnologies are particularly vulnerable to weaknesses in process patent protection because it is often the only protection available for a human gene product isolated or produced using biotechnology. A forthcoming OTA report on *Patenting Life* will examine these process patent issues, as well as those surrounding the patenting of whole animals engineered to produce human gene products with therapeutic potential.

Access to Biotechnology Information

Rapid advances in recombinant DNA and other biotechnologies have caused an information explosion in the biological sciences. The relentless pace of new developments in biotechnology parallels that of information processing, storage, and retrieval. The combination of developments from these two high-technology sectors could lead to even greater advances. Access to information generated by biotechnology is crucial to innovation. Organization of the data generated in biotechnology research is necessary for researchers in the participating scientific disciplines (e.g., microbiology, biochemistry, immunology etc.) to build on their individual contributions. Biotechnology information access and organization has implications in several areas of national policy, such as:

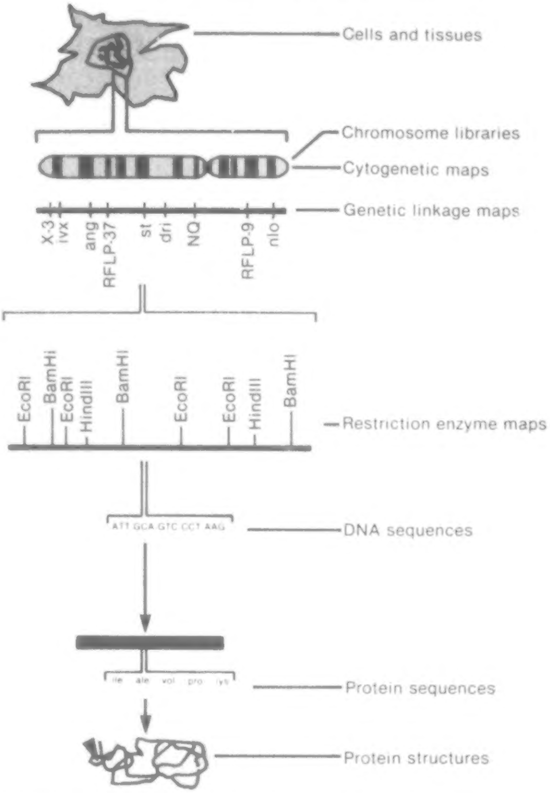
- regulation of commercial products of biotechnology;
- support of biotechnology research and development;
- public perception and awarenesss of biotechnology;
- intellectual property rights; and
- coordination among Federal agencies (39).

This section focuses on how information access and organization is vital to continued advances in the application of biotechnology to medicine.

A National Research Council report (39) urged that Federal agencies supporting biotechnology research continue to fund or initiate funding in activities concerning biotechnology information. These efforts could range from developing relevant computer software to national centers for information networks. Another recommendation was that the National Library of Medicine (NLM) at the National Institutes of Health coordinate a "database of databases" for biotechnology information and expand its role as an information resource center. Implementation would require an expansion of the current NLM directory of information sources (DIRLINE) and would include a cross-referencing system and a thesaurus for biotechnology. The users of these facilities would not only be the researchers in the multiple scientific disciplines involved, but regulators, patent attorneys, and other officials needing information on biotechnology. Congress appropriated $3.83 million in fiscal year 1988 for the NLM to initiate work on the proposed database of databases.

There are more than a hundred different databases—some more frequently used than others—maintained as sources of data for researchers in the various biological sciences (12). There are databases containing the nucleotide sequences of cloned genes, the amino acid sequences of proteins, the structures of organic molecules, locations of genes on chromosomal maps, pedigree data from families with genetic diseases, and three-dimensional atomic coordinates of protein structures (figure 9-6). Computer software has been developed that allows a researcher to analyze his or her own data relative to that stored in the databases. The Division of Research Resources at NIH funds a national computer resource, called BIONET, that offers sophisticated analytical software for use by government and academic researchers (industry only has access to the BIONET information network). Databases of structures of nonbiologic drugs with established activity can be used together with those containing three-dimensional structure data on proteins in rational drug design strategies. Research on the structure of one of the family of viruses that cause acquired

Figure 9-6.—Databases in Biotechnology



SOURCE: The National Library of Medicine and Office of Technology Assessment, 1988.

immune deficiency syndrome was made feasible by the BIONET resource (60).

In 1987, a group of government, academic, and industrial scientists met in Santa Fe, NM to develop a strategy for making biological information accessible to all users. Their goal is to create an expert system, called the Matrix of Biological Knowledge, by interconnecting available databases in ways that will interpret the scientific questions of investigators from any one of a number of diverse fields in biology and chemistry (36). The NLM database of databases would be only one component of the system. Through the Matrix system, a pharmaceutical scientist would be able to communicate on-line with the data from the work of agricultural scientists, for example. Certain task groups have been set up to initiate small projects that would demonstrate the efficacy of Matrix, with the hope of gaining additional support for the project (68).

The transfer of information from proprietary sources to the public domain is an important public policy issue. For example, scientists from both the public and private sectors are conducting research aimed at elucidating the structure and function of human genes and gene products. **Ready access to information, as it evolves, is essential for maintaining the current pace of innovation in areas of biotechnology that could improve human health and prevent disease. This will require the timely entry of information (proprietary and otherwise) into public databases** (53).

Availability of Trained Personnel

The availability of trained personnel has been indispensable to the dominant position maintained by the United States in pharmaceutical biotechnology. There is a wide variety of scientific and administrative personnel who perform the work involved in applying biotechnology to the discovery and commercialization of human therapeutics. Scientists who carry out basic research, process engineers responsible for product scale-up, pharmacologists and clinicians who perform studies in animals and humans, legal and regulatory administrators who must apply existing law to the products and processes of biotechnology, and marketing personnel are all involved. Chapter 8 covers the general scientific training and personnel needs of both academia and industry. Chapter 6 addresses the problems in obtaining and keeping highly trained scientific personnel in the various government agencies. This section summarizes the research disciplines from which highly trained scientists must continue to emerge to fill the existing gaps in biotechnology research along the path to development of new human therapeutic products.

In a recent report, the National Academy of Sciences (NAS) (38) requested increased Federal attention to the need for interdisciplinary training in biology, chemistry, and physics for graduate students and postdoctoral personnel. The new generation of structural biologists, those who will be primarily responsible for advances in protein engineering and rational drug design, must be trained in the basics of protein chemistry, molecular biology, and biophysics. An increasing number of large corporations and dedicated biotechnology companies have set up programs to study the three-dimensional structure of large molecules such as proteins and DNA. These programs require expertise in such biophysical methods as x-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), theoretical molecular modeling, and computer graphics. While the fields of molecular and cellular biology are well populated ([illegible]3), academia and industry (especially pharmaceutical companies) are competing for scientists trained in structural biology (23).

As the number of cloned human genes rises, and the ability to purify their protein products increases, there will be a growing need for scientists trained to determine how these proteins work in the human body, and to assess their potential as human therapeutics. This would require researchers from the traditional fields of human physiology, pharmacology, and toxicology, but with experience that extends beyond traditional synthetic drugs to include protein drugs.

In assessing personnel and training program needs, it is important to emphasize that as biotechnology becomes fully integrated into biomedical research, and new research tools continue to be developed, the types of scientific expertise required will also evolve. Therefore, **scientists with solid training in the general areas of biology, chemistry, and computer science will likely be the best prepared to meet the changing needs of biomedical R&D in both academia and industry.**

FUTURE APPLICATIONS OF BIOTECHNOLOGY TO HUMAN THERAPEUTICS

Some scientists believe that the use of biotechnology will actually contribute more to studies aimed at understanding the basic processes underlying cellular physiology than to the production of novel human therapeutics. In other words, once the mechanisms directing normal cellular functions are known, conventional drugs (e.g., pharmaceuticals made by chemical synthesis) may be designed more intelligently (or rationally) because the chemical characteristics of their target sites and their mechanism of action will be better understood (6). Biotechnology has stimulated the interest of pharmaceutical companies in rational drug design, but research in this area is expensive, requiring multidisciplinary research teams and costly instrumentation and computers for designing molecules. Despite the renewed enthusiasm in this area, computers and molecular modeling have led to very few rational drug design successes (43,62). Therefore, for the time being, these methods are more likely to remain in academic laboratories and a few large pharmaceutical companies, than in the smaller companies dedicated to biotechnology.

One strategic challenge posed by human therapeutics made using biotechnology is that new methodologies are constantly being developed that improve product purity, stability, and production efficiency, and manufacturing processes must be modified accordingly. For example, Genentech, Inc. modified its manufacturing protocol for TPA during clinical trials, making it necessary to ascertain any effects unique to the product manufactured by the new process (47,71). In such circumstances, the sponsor is faced with the obvious benefits of rapid advances in molecular biology and the desire to design a superior product against the financial and regulatory burdens incurred by altering manufacturing processes during development (4). In contrast to the scenario for conventional drugs where manufacturing records establish the criteria for product purity, for human therapeutics made using biotechnology, the process also plays a role in defining the regulatory guidelines for the products (57,58). For therapeutic applications in which biotechnology is not the only option for product development, these factors will continue to influence the choice between biotechnology and more conventional routes.

ISSUES AND OPTIONS

ISSUE 1: Should action be taken to ensure that the development incentives provided in the Orphan Drug Act are being used for their intended purposes?

The objective of the Act was to provide incentives for developing drugs for rare diseases that would not otherwise be developed because the anticipated financial rewards were insufficient. The simultaneous development of an orphan product by multiple companies implies either that the potential commercial value of the product is high enough that it would be developed even without the Orphan Drug Act incentives, or that the companies are unaware of each other's development activities. Therefore, if Congress takes measures to amend the provisions of the Act to prevent improper use of its objectives, it should do so taking care not to remove incentives for the majority of sponsors who are developing drugs that are truly orphans.

Option 1.1: Take no action.

The Orphan Products Board reported a significant increase in orphan drug development, including a substantial number of products made using biotechnology (over 10 percent of the total) in the five years since the Act. Dedicated biotechnology companies have limited resources to invest, and they generally aim their R&D budgets at potentially profitable drugs. If the existing incentives for R&D investment in orphan drug applications were altered, the dedicated biotechnology companies might be less likely to participate in orphan drug development than would the large, established corporations. However, the smaller companies have contributed much to innovation in the development of biotechnology products, and for some orphan diseases, these could prove to be the only effective products. Congress could thus determine that the tax credit and 7-year market exclusivity incentives of the Act are, for the most part, being used as designed, and that no further action is necessary.

Option 1.2: Amend the Orphan Drug Act to discourage sponsors from using orphan drug status as a means of achieving market exclusivity for drugs that they would likely develop without the incentives of the Act.

The 7-year market exclusivity provision of the Act was intended to assure orphan drug developers that they would recoup their development costs, even though there was little commercial value and inadequate patent protection for the product. Concern has been raised that in the face of uncertainty over the validity and scope of patent protection on many biotechnology products, the developers are viewing the Act's market exclusivity provision as a patent substitute. Therefore, in keeping with the legislative intent of the Act, measures could be taken to ensure that its incentives are not abused by sponsors who stand to make substantial financial gains on orphan products. One or a combination of any of the following options could be used by Congress to amend the market exclusivity provisions of the Orphan Drug Act:

- Orphan drug sponsors with pending patent applications, or holding patents with lifetimes that will not expire soon after market approval, could be excluded from 7-year market exclusivity rights.
- Any company willing to carry out all of the necessary testing of a drug identical to or similar to one already approved for the same disease could market their product during the 7-year protection period afforded to the company that originally developed the drug.
- A 7-year term of market exclusivity could be granted to all companies that had filed NDAs or PLAs for the same therapeutic use of the orphan product by the time market approval was granted to the first company. Congress might find that this option balances the need to continue proven incentives for orphan drug development with both the equitable treatment of codevelopers of a particular drug and competition in the major markets that can support it. If market exclusivity is shared only by companies that have already filed an NDA or PLA at the time the first application is approved, then companies only days away could be excluded, even though they had made significant investments in orphan drug development.
- The market exclusivity provision could be removed. Congress could determine that the low profitability of drugs marketed for orphan uses offers a natural market exclusivity to the original developer in most cases, thereby superceding the need for such a provision. Without the provision, however, there would be no assurance that the sponsor of a product that is either off patent or unpatentable, could offset some or all of the development costs by recouping all possible revenues from the sale of the drug. Moreover, exercising this option would remove incentives for all orphan product developers, even though only a few products, such as recombinant DNA-derived human growth hormone and erythropoietin, could yield substantial revenues.
- Sponsors receiving revenues from sales of orphan drugs for rare disease applications that exceed a fixed ceiling could lose their market exclusivity rights. Congress could find that this approach is the most direct one for discouraging the use of the development incen-

tives offered by the Act for drugs with anticipated profitability.

ISSUE 2: Should Congress act to facilitate access to information generated by biotechnology-based research with potential applications to human health?

Rapid advances in recombinant DNA, hybridoma, and other biotechnologies have led to an explosion of information in the biological sciences. Organization of the data generated in research based on biotechnology is necessary for building on individual contributions and furthering innovation. Databases exist in government and academic laboratories for a wide variety of biological information; some of the databases, such as those containing DNA and protein sequences, are heavily used, while others are used by individuals in more specialized fields. In some cases, databases are used to indicate the availability of and to describe certain types of biological materials. The users of biotechnology information are not only academic, government, or industrial researchers, but regulators, patent attorneys, and other officials needing data.

Option 2.1: Take no action.

The National Institutes of Health, through the Division of Research Resources and other categorical institutes, maintain over 100 informational databases, and fund research for managing and understanding large amounts of biological information. Congress could conclude that these NIH activities, and those of other Federal agencies are sufficient to meet the major needs in biotechnology information management. However, many scientists view the existing resources for assimilating and analyzing the rapidly accumulating biotechnology information as insufficient to meet the needs of the community of users.

Option 2.2: Increase funding levels for existing programs or initiate funding in new activities concerning biotechnology information management.

The development of computer software to link the large number of different databases in a way that will allow researchers to better analyze their own data, and to avoid unnecessary duplication of research, is a major goal of all researchers using biotechnology. Congress could authorize Federal agencies that support biotechnology research to fund more activities related to the development of new systems for managing biotechnology information. These efforts could range from developing relevant computer software to national centers for information networks. The designation or creation of a center or centers for biotechnology information analysis and management could assist in the development of new communication tools and serve as centers for the distribution of biological information.

The National Library of Medicine (NLM) is one possible location for a biotechnology information center. The NLM has made a catalog of human genetic loci, called Mendelian Inheritance in Man, available on line through its Information Retrieval Experiment (IRX) program, and has linked the data in this volume to the information available in GenBank® and the Protein Information Resource databank (funded primarily by NIH), to important databases for researchers in molecular biology. The NLM has also begun an experimental program for linking molecular biology databases, using researchers at NIH to test the system's effectiveness.

SUMMARY

The pharmaceutical industry enjoys the highest level of biotechnology R&D investment from both public and private sources. In fiscal year 1987, the National Institutes of Health, with its research mission in human health and disease prevention, provided about 20 times the amount of any other Federal agency on biotechnology R&D. Companies developing human therapeutics based on biotechnology had R&D budgets higher than those financed by any other industrial sector in the 1986/1987 fiscal years. Human therapeutics make up the primary R&D effort of 21 percent of dedicated biotechnology companies and 26 percent of the larger, established corporations using biotechnology. Because the application of biotechnology to the development of human therapeutics has only recently begun to make the transition from new technology development to successful clinical applications, the availability of funds for basic and applied research will be important in sustaining the current pace of product development.

The rate of human therapeutic product development could be substantially increased if greater effort were given to developing new methods to isolate genes and proteins for research; establish relationships between protein structure and function; determine how proteins fold into active structures; study the physiological roles of human proteins in model systems; analyze the mechanisms of protein maturation and export from cells; and deliver human therapeutic proteins to the appropriate targets in the human body. Despite its successes in the area of human therapeutics, however, biotechnology will likely only complement more traditional methods of isolating or synthesizing pharmaceuticals.

The new biotechnologies are now an integral part of research in the development of human therapeutics at dedicated biotechnology companies and at larger, more established pharmaceutical corporations. Biotechnology is now being applied by the pharmaceutical industry as a tool for developing therapies for many different human diseases and afflictions. A company's success in applying biotechnology to the development of human therapeutics will now be measured not just by its research capabilities, but also by its strengths in meeting drug approval requirements, protecting intellectual property rights, and new product marketing. **There is no longer a clear advantage of the dedicated biotechnology companies over the pharmaceutical industry giants in the development of new products and processes. On the other hand, the large, established companies can no longer claim a substantial lead in the management end of product development.**

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Chapter 10

U.S. Investment in Biotechnology Applied to Plant Agriculture

"Let us never forget that the cultivation of the earth is the most important labor of man."

—Daniel Webster
January 13, 1840

". . . whoever could make two ears of corn, or two blades of grass, to grow upon a spot of ground where only one grew before, would deserve better of mankind, and do more essential service to his country, than the whole race of politicians put together."

—Swift
Gulliver's Travels: Voyage to Brobdingnag

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Chapter 10

U.S. Investment in Biotechnology Applied to Plant Agriculture

Agricultural research in the United States is not monolithic. It uses both traditional methods, such as plant and animal breeding, and newer biotechniques, such as genetic engineering. It spans a broad range of applications, extending from livestock to fisheries to crops to forests to microorganisms. U.S. agricultural research is a longstanding institution with public and private sector components. **And, while it is often difficult to compartmentalize the diverse components of agricultural research, this chapter focuses on U.S. investment—both human and financial capital—in biotechnological research of plants in agriculture. Who invests in plant agricultural biotechnology research, and what factors influence the amount invested and how the funding is used? What actions are necessary to enhance the development of agricultural research?**

An analysis of plant biotechnology research must include a discussion of the firmly established (and necessary) traditional technology component, i.e., plant breeding. Thus, while this chapter focuses on biotechnological applications, it examines, to a lesser extent, the delicate balance between research with the new techniques v. traditional agricultural research. Because it is difficult to separate research activity from commercial development in plant biotechnology, this chapter first examines factors influencing investment in U.S. plant agricultural research, and then briefly examines issues important to commercialization of such research.

This chapter principally examines investment in plant agricultural biotechnology and issues that affect the dollar flow (rather than, for example, the impact of biotechnology on farms or on the extension service). A comprehensive analysis of biotechnology and its impact on the infrastructure of American agriculture was assessed in the 1986 OTA report *Technology, Public Policy, and the Changing Structure of American Agriculture* (101). While micro-organisms play a pivotal role in plant biotechnology research and development (R&D), examining micro-organismal applications is beyond the scope of this chapter. Finally, although plant agricultural applications of biotechnology play a central role in discussions about environmental risks of biotechnology, these issues are addressed in a separate OTA report in this series (96).

FACTORS INFLUENCING U.S. INVESTMENT IN AGRICULTURAL RESEARCH

U.S. agriculture—plant and animal—is one of the most efficient and productive sectors in this country's economy. Despite declines in recent years, the U.S. agricultural trade balance has added a surplus to the U.S. trade account every year since 1960 (91,101). Agriculture contributes to, directly or indirectly, approximately 20 percent of the gross national product, 23 percent of the nation's employment, and 19 percent of export earnings (77).

Increasingly, however, myriad problems beset U.S. agriculture. Complex in nature and scope, they include the declining competitive position of U.S. agricultural products in international markets, increasing commodity surpluses, low profitability for significant numbers of farmers, and environmental effects of agrichemicals (83,102). Research alone cannot solve these problems, but can contribute to their solution if resources, human and financial, are available (83,102). Thus, **although the problems facing agriculture are serious, the impact of Federal R&D in this sector in particular can be powerful** (100).

The benefits of agricultural research are substantial. The U.S. Department of Agriculture (USDA) claims the annual rate of return for investment in agricultural research is between 30 and 50 percent per year (83,104). Other estimates of rate of return vary from 21 percent to 110 percent, with the vast majority in the 33 to 66 percent range (100). **In particular, biotechnology products are expected to improve international competitiveness of U.S. agricultural products** (101).

Over the past decade and a half, however, the U.S. agricultural research system has undergone increased scrutiny and criticism (66,48,81). Agricultural research endeavors, including biotechnological applications, are presently in a state of flux. Several factors affect, or have affected, the investment forecast for agri-biotechnological research, including:

- the discovery of the new technologies themselves,
- intellectual property rights for plants,
- the funding source of plant agricultural biotechnology research,
- the regulatory environment,
- domestic political and economic conditions, and
- international markets.

With such a range of pressures, the emphasis in U.S. plant biotechnology constantly shifts to derive the optimum formula to achieve the maximum return possible. The following sections focus on how investment in plant agricultural research responded or is responding to the first three factors: the advent of the biotechniques; plant ownership; and private v. public plant research funding.

THE BIOTECHNIQUES IN AGRICULTURAL RESEARCH

New biotechnologies have the potential to modify plants so that they can resist insects and disease, grow in harsh environments, provide their own nitrogen fertilizer, or be more nutritious. Technical barriers, however, still exist. In particular, widespread success in applications for multigenic traits (such as salt tolerance or stress resistance) will for the present remain elusive (17,44), perhaps decades away (6,101). Nevertheless, the newer technologies can potentially lower costs and accelerate the rate, precision, reliability, and scope of improvements beyond that possible by traditional plant breeding (68,101).

Two broad classes of biotechniques—cell culture and recombinant DNA—are likely to have an impact on the production of new plant varieties. Plant tissue and cell culture date from the turn of the century, but were only minimally exploited until the late 1950s (6). Successful in vitro cultivation of plant cells and related culturing techniques underlie today's gene transfer techniques and subsequent regeneration of altered, whole plants. Plant tissue and cell culture are also critical tools for increasing fundamental knowledge through basic research. The history of genetic engineering and a detailed description of the principles of recombinant DNA technology are discussed in an earlier OTA report in this series (97). In general, the fundamentals of genetic engineering are similar for microbial, animal, and plant applications, but developing some new approaches for plant systems has been necessary.

The endpoints of crop improvement using biotechnology are those of traditional breeding: increased yield, improved qualitative traits, and reduced labor and production costs. New products not previously associated with classical methods also appear possible. Box 10-A briefly describes some of the new biotechniques exploited to achieve these aims. Comprehensive descriptions of strategies designed to transfer foreign genes to plants and plant cells have been published elsewhere (19,21,57,67,68,70,88).

Applications of the Techniques

The new biotechniques are useful for investigating diverse problems and plant types. For example, plant tissue and cell culture is an important technique for breeders. It can be used for screening, at the cellular level, potentially useful traits. As many as ten million cell aggregates can be cultured in a single 250 ml flask (less than 1 cup). This can be compared to a space require-

Box 10-A.—Techniques Used in Plant Biotechnology

Plant Tissue and Cell Culture. Plant cultures can be started from single cells, or pieces of plant tissue. Cultures are grown on solid or in liquid media. Several species of plants, including alfalfa, blueberry, carrot, corn, rice, soybean, sunflower, tobacco, tomato, and wheat, can be cultured in vitro (3).

Plant Regeneration. Regenerating intact, viable organisms from single cells, protoplasts, or tissue is unique to plants and pivotal to successful genetic engineering of crop species. (To produce a protoplast, scientists use enzymes to digest away the plant cell wall.) Although genes can be transferred and examined in laboratory cultures, ultimate success is achieved only if the culture can be regenerated and the characteristic expressed in the whole plant. Figure 10-1 illustrates steps involved in regenerating plants in vitro.

Protoplast Fusion. Protoplasts from different parent cells are artificially fused to form a single hybrid cell with the genetic material from each parent. Protoplast fusions are useful for transferring multigenic traits or for fusing cells from plants that cannot be crossed sexually (68), thus permitting the exchange of genetic information beyond natural breeding barriers. Successful gene transfer via protoplast fusion depends on the ability to regenerate a mature plant from the fusion product.

***Agrobacterium tumefaciens* plasmid.** One of the most widely used and probably the best characterized system for transferring foreign genes into plant cells is *Ti* plasmid-mediated transfer (88). The technique involves a plasmid vector (*Ti* plasmid) isolated from *Agrobacterium tumefaciens*, a naturally occurring soil-borne bacteria that can introduce genetic information stably into certain plant cells in nature. Using recombinant DNA technology, the plasmid has been modified to increase its efficacy in the laboratory.

Transformation (Direct DNA Uptake). Certain chemical or electrical treatments allow direct uptake and incorporation of foreign DNA into plant protoplasts—a process called transformation. Since hundreds of thousands of cells can be simultaneously treated, transformation is a relatively easy technique. Cells expressing the desired trait can be regenerated and tested further.

Microinjection. Using a special apparatus, fine glass micropipettes, and a microscope, DNA is directly introduced into individual cells or cell nuclei (in plants, protoplasts are usually used). The process is more labor-intensive than transformation, requiring a trained worker. Although fewer cells can be injected with DNA than in mass transformation, a higher frequency of successful uptake and incorporation of the foreign genetic material can be achieved (68)—up to 14 percent of injected cells (22).

Virus-Mediated Transfer. Virus-mediated transfer of DNA has played a critical role in nonplant applications of biotechnology. But in large part due to an underdeveloped knowledge base, viral vectors for plant systems generally have not been exploited (68). Cauliflower mosaic virus has been used with some success in turnips (14,68), and Brome mosaic virus in barley (35,68). Developing generic virus-mediated transfer systems could accelerate progress in plant biotechnology.

DNA Shotgun. One novel approach uses gunpowder to deliver DNA into plant cells (54). The DNA to be transferred is put onto the surface of four micrometer tungsten particles and propelled into a plant cell by a specially designed gun. Figure 10-2 is a photograph of an onion cell with such microprojectiles visible within its confines. While an innovative approach, it is unclear whether it will prove to be a routine method for gene transfer in monocots (15).

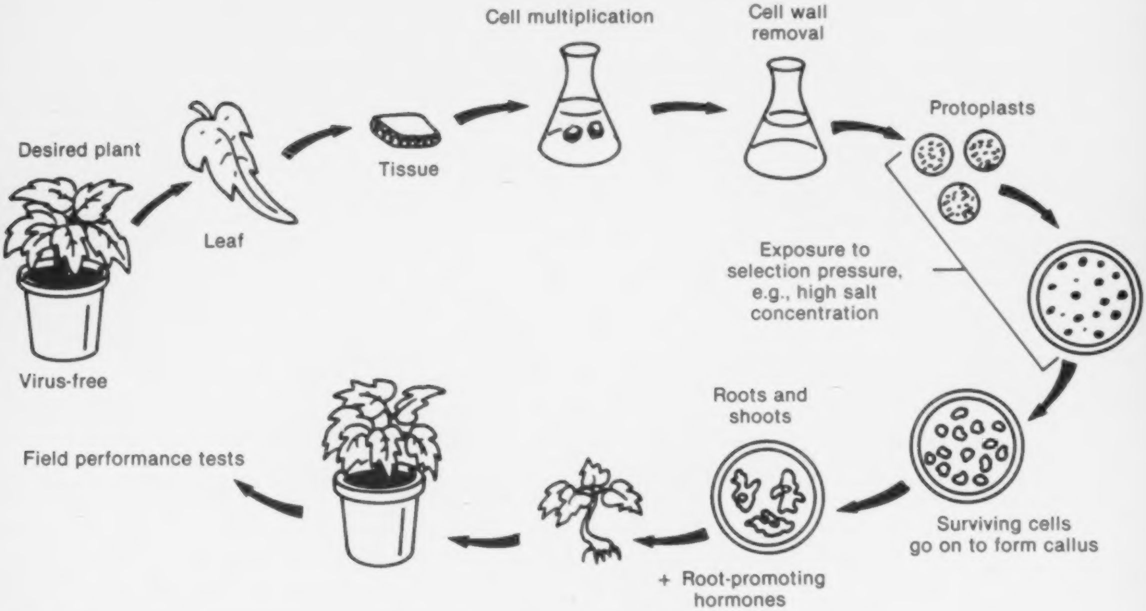
SOURCE: Office of Technology Assessment, 1988.

ment of 10 to 100 acres if individual test plants were put into the field (6).

Several species of plants can be clonally regenerated to produce genetically identical copies. The process is widely used for a range of commercial applications, including forestry and horticulture (e.g., producing strawberry, apple, plum, and peach plants). Several crop species, such as asparagus, cabbage, citrus, sunflower, carrot, alfalfa, tomatoes, and tobacco are also routinely regenerated (94). Although monocotyledonous plants, such as the cereals, have been more difficult to

Figure 10-1.—Plant Propagation: From Single Cells to Whole Plants

The process of plant regeneration from single cells in culture


Desired plant
Virus-free
Leaf
Tissue
Cell multiplication
Cell wall
removal
Protoplasts
Exposure to
selection pressure,
e.g., high salt
concentration
Surviving cells
go on to form callus
Roots and
shoots
+ Root-promoting
hormones
Field performance tests

The process of plant regeneration from single cells or plant tissue in culture.

SOURCE: Office of Technology Assessment, 1988.

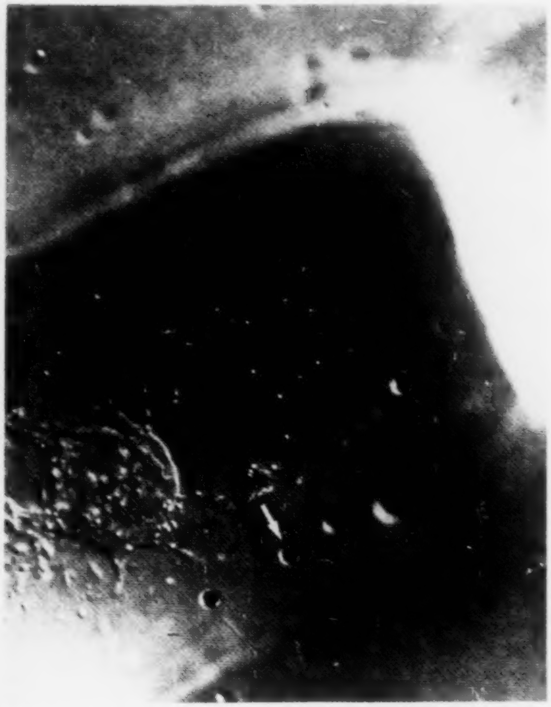
regenerate, rapid progress is being made with these as well (1,37).

Plant regeneration is a powerful tool not only for increasing the numbers of propagated materials, but also for reducing the time required to select for genetically interesting traits. Furthermore, under certain conditions, genetic variants arise during the culturing process (somoclonal variation). Somoclonal variation can uncover new, useful variants and again reduce the time spent selecting genetically interesting traits.

Many important agricultural applications of biotechnology depend on regenerating whole plants from protoplasts. Protoplast fusion has been applied successfully in several plants, including the potato. In this instance, cells from wild and cultivated potato plants were fused to transfer the viral resistance of the wild species. The hybrid cells were regenerated into fertile plants that expressed the desired virus-resistant characteristic (12,68). Virus-free potato cells can now be cultured in vitro, and virus-free plants regenerated; the yield of these plants has increased substantially (107). Culturing virus-free plant cells is particularly important in certain horticulturally important species, including ornamentals and certain vegetable crops. As is the case with single cell or tissue regeneration, protoplasts of the monocotyledonous subclass of plants, such as cereals, have been much more difficult to regenerate than protoplasts of the other major plant subclass, dicotyledonous plants, such as tobacco and tomato.

Ti vectors are especially useful for genetically engineering dicotyledonous plants, such as tobacco, tomato, potato, and sunflower. For example, *Ti*-mediated transfer has been used to engineer virus-resistant tobacco plants (38,46) and insect-tolerant tomato plants (33) (figure 10-3). The technique is less useful for gene transfer in monocots (which include important cereal crops). Increas-

Figure 10-2.—Onion Cell Bombarded With DNA-Microprojectiles

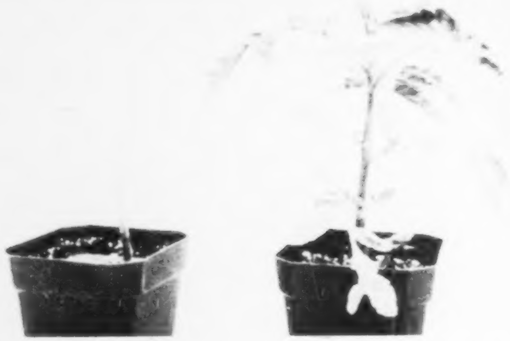


DNA is precipitated onto the surface of 4 μm tungsten particles. A gunpowder charge in a specially designed gun detonates the firing pin that accelerates the projectiles into the onion cells. The cells remain viable if the number of particles per cell remains below 20. The DNA delivered to the cells via the particles is expressed. Three projectiles can be seen in this photograph.

SOURCE: T.M. Klein, E.D. Wolf, R. Wu, et al., "High-Velocity Microprojectiles for Delivering Nucleic Acids Into Living Cells," *Nature* 327:70-73, 1987. Reprinted by permission from *Nature*, Copyright © 1987 Macmillan Journals Ltd.

ingly, however, technical hurdles identified as barriers only a few years ago (94,101) are being cleared (1,24,43). Recent success using the *Ti* vector for corn (a monocot) has been reported (43), with continued progress for monocots anticipated (108). Furthermore, direct DNA transformation apparently allows gene transfer in several cereals (monocots), including rice, wheat, and maize, with an efficiency approaching comparability to the frequency of *Ti*-mediated gene transfer in dicots (19).

Figure 10-3.—Genetically Engineered Insect-Tolerant Tomato Plant



Larvae were allowed to feed on a transgenic tomato plant (right) and a normal plant (left). After seven days, the plant that was genetically engineered for tolerance to the insect is still relatively intact, whereas the normal plant has been destroyed.

Photo credit: Monsanto Corp.

New applications and new techniques, such as the "DNA plant shotgun," (54) are continuously arising. Table 10-1 describes a few recent applications of biotechnology to plant agriculture.

Impact of Biotechniques on Agricultural Research Investment

In part, the advent of genetic engineering and related biotechniques has, itself, altered the shape and scope of U.S. agricultural research investment decisions (17,56). In particular, the emerging technologies presented fundamental challenges and opportunities for the public component of U.S. agricultural research (17). Basic science advocates charged that the USDA-led system had not been on the cutting edge of science nor had been paying enough attention to basic research (66,81), stimulating an evaluation of the system that continues today.

Some have argued that the biotechnologies have led to private sector, proprietary-dominated research efforts. Others, however, point out that increased private sector research investment resulting from the biotechnology boom has uniquely contributed to the fundamental knowledge base

Table 10-1.—Some Recent Applications of Biotechnology to Plant Agriculture

Rice: Whole rice plants can be regenerated from single-cell protoplasts; recent advances that improve the efficiency of the process are important to progress in applying genetic engineering to cereals in general (1,37).

Maize: The *Ti* vector was recently used to transfer the maize streak virus into corn plants, a monocotyledonous member of the grass family. The study is a landmark because the *Ti* plasmid is probably the best characterized plant vector and an efficient gene transfer mechanism, but monocots had been refractory to its use (43). Successful plant regeneration of maize protoplasts also was reported recently (80).

Rye: Using a syringe, DNA was injected into rye floral tillers. The new genetic material was introduced into the germ cells of this monocot, and some recovered seeds grew into normal plants that expressed the foreign gene. This simple strategy, which does not require plant regeneration from protoplasts, could be useful in other cereals (24).

Orange: Orange juice-sac cells have been removed from mature fruit and maintained in tissue culture. The cells produce juice chemically similar to that squeezed from tree-grown fruit. Such laboratory cultivation could advance trait selection and speed up varietal development, although laboratory produced juice is not on the immediate horizon (34).

Tomato: A gene that confers a type of insect tolerance was recently transferred via the *Ti* system to tomato plants. The tolerance is also expressed in progeny plants. Since over $400 million per year is spent to control this type of pest, constructing insect transgenic plants of this sort is of great interest to the agricultural community (33). See also fig. 10-3.

SOURCE: Office of Technology Assessment, 1988.

and resulted in a positive economic impact (47). And, through increasing alliances between companies and universities, industry involvement has also resulted in resources for new ideas, with potential to further enhance economic return through accelerated technology transfer (47).

Biotechnology has also stimulated greater interest in agricultural research by the nontraditional agricultural research community. Today, agricultural applications command greater interest within the general research hierarchy (23,42,89). While some believe this shift is valuable (42), others fear that research directed to address regional and local problems could suffer and that "have" and "have not" institutions will result (27,52,53,58,101).

In addition to the effect of biotechnology on research investment decisions, concern has been raised about biotechnology's influence on investment in human capital: namely, a decline in the number of full-time equivalents (FTEs) in traditional plant breeding at the expensive of increasing numbers of FTEs in molecular biology (44,58). Improvements in varieties with the new biotechniques will be hollow achievements if there is a shortage of traditional plant breeders who conduct the complementary field research that is essential to develop varieties for use by farmers. Some reports indicate a 15 to 30 percent decrease in university-based plant breeders and an increase of about one-third in molecular biologists between 1982 and 1985 (59). This trend might, in part, reflect the glamour image of plant molecular biology coupled with industrial demands for plant breeders (36).

A continuing industry demand for trained plant breeders might be an attractive argument for those making career decisions and ensure an adequate supply of plant breeders (42). However, a large majority of graduate students in the plant sciences still want to work in molecular biology, and siphoning university plant breeders to industry could leave a teaching void for those who want to learn conventional breeding (44). At present, some argue that a balance in supply seems to have been (or is being) struck (36,74). Others within industry and academia assert a lack of plant breeders exists (29,44). Regardless, evidence for both sides is largely anecdotal, and accurate accounting would be useful for forecasting and planning the direction of plant agricultural research.

The impact of the biotechnologies on the direction of agricultural research has not, however, occurred in a vacuum. Intellectual property issues and who funds projects also are important factors. For example, the concern about the exchange of plant-breeding materials just mentioned has been generated both by the research thrust using the biotechnologies and interpretation of patent law (44). The biotechniques have also contributed to an evolution in the investment emphasis (i.e., the types of projects funded) of private and public sources. The impact of these two issues, property rights and funding source, on research investment is examined in following sections.

PROPERTY RIGHTS AND PLANTS

Proprietary protection of plants precedes recombinant DNA technology by about four decades. Today, two Federal statutes specifically confer ownership rights to new plant varieties: the Plant Patent Act of 1930 (35 U.S.C. §§161-164) and the Plant Variety Protection Act of 1970 (7 U.S.C. §2321 et seq.). The *Chakrabarty* decision coupled with *Ex parte Hibberd* (32) affords plant breeders the additional option of seeking a utility patent (35 U.S.C. §101) to protect a novel variety.[1]

The following sections first outline the laws relevant to plant property and hybrid plants, and then analyze the effect plant protection has had on U.S. investment in agri-biotechnology. A detailed analysis of plant protection and its economic consequences will be explored in a forthcoming OTA report, *New Developments in Biotechnology: Patenting Life*. The issue of intellectual property as a barrier to commercializing plant products is briefly discussed later in this chapter.

Plant Patent Act of 1930 and Plant Variety Protection Act of 1970

In 1930, Congress passed the Plant Patent Act (PPA), allowing patent protection for new and distinct asexually propagated varieties other than tuber-propagated plants. PPA, administered by the U.S. Patent and Trademark Office, gives the patent holder the right to exclude others from asexually reproducing the plant or from using or selling any plants so reproduced, for a period of 17 years. At the time PPA was enacted, it was not thought possible to produce stable, uniform lines via sexual reproduction (4). These ideas were revised, however, and Congress passed the Plant Variety Protection Act (PVPA) in 1970.

PVPA provides for patent-like protection to new, distinct, uniform, and stable varieties of plants that are reproduced sexually, except fungi, bacteria, tuber-propagated plants, uncultivated plants, and first-generation hybrids. The breeder may exclude others from selling, offering for sale, reproducing (sexually or asexually), importing, or exporting the protected variety. In addition, others cannot use it to produce a hybrid or a different variety for sale. However, saving seed for crop production and for the use and reproduction of protected varieties for research is expressly permitted. The period of exclusion is 18 years for woody plants and 17 years for other varieties. PVPA is administered by the Plant Variety Protection Office, USDA.

Diamond v. Chakrabarty

In the landmark case *Diamond* v. *Chakrabarty*, the U.S. Supreme Court addressed one of the major patent law questions arising from applications of the new biotechniques—whether living, human-made micro-organisms are patentable (25). In a 5 to 4 decision, the Court made it clear that the question of whether or not an invention embraces living matter is irrelevant to the issue of patentability, as long as the invention results from human intervention. Since 1985, when the Patent Office ruled that utility patents could be granted for novel plants (32), genetically engineered plants have been granted utility patents. There are no exemptions for a plant utility patent—in contrast to PVPA, the holder of a plant utility patent can exclude others from using the patented variety to develop new varieties.

Impact of Intellectual Property on Agricultural Research Investment

Intellectual property and plant protection have influenced and continue to influence the direction of U.S. plant agricultural research investment. Since the enactment of PVPA and the *Chakrabarty* decision, private sector interest has blossomed (101). Funding to initially capitalize dedicated biotechnology companies (DBCs) was based, in some measure, on the expectation that legal means existed to protect discoveries resulting from the investment. In particular, some view the option of applying for plant utility patents (afforded by *Chakrabarty* and *Hibberd*) as sparking progress and increasing dollar flow in the industry by providing both the scope of protection needed to encourage new research investment and the rapid dissemination of information describing the new technology resulting from the research (109).

---

[1] Trade secrets are also an important form of plant protection. In particular, the hybrid seed industry (such as corn) makes extensive use of trade secrets (36). Hybrid seeds have "internal genetic protection," making them more amenable to the trade secret approach (27). Inbred parental lines (trade secrets themselves) are crossbred to produce high-yielding hybrid seed (also trade secrets) with "hybrid vigor." But, unlike seed for nonhybrid crops, seed from a harvest using hybrid seed cannot be saved and used for additional high-yield planting cycles. Since hybrid vigor from subsequent progeny declines, the producer must return to the source for new seed to maintain the highest yields. Thus, the genetics of hybrid seed *de facto* force the producer back to the supplier, and the hybrid seed industry has preferred trade secret plant protection, rather than seeking monetary return through the certificate or patent process (each with disclosure requirements) (26). Academic researchers probably view trade secrets less favorably, since they hinder publication efforts (94).

In contrast with the *Chakrabarty* decision, the role of PVPA in directly stimulating private investment is less clear (18). Some argue that the rate of private research investment in plant breeding following passage of PVPA equals that during the preceding decade (55). However, others dispute the notion that private investment has not risen since passage of PVPA in 1970 (61,63). The perception, however, that PVPA would increase the profitability of seed companies galvanized far-reaching acquisition and merger activity involving many American and international companies (18,55). These corporate entities were then poised to take advantage as events in the biotechnology revolution unfolded.

Plant protection is not only important to commercial parties, but to public sector institutions as well. Until 1980, only about 4 percent of some 30,000 government-owned patents were licensed (73). Furthermore, the government policy of granting nonexclusive licenses discouraged investment, since a company lacking an exclusive license was reluctant to pay the cost of developing a product and building a production facility. Potentially valuable research thus remained unexploited. Congressional concern about this innovation lag prompted passage in 1980 of the Patent and Trademark Amendment Act (Public Law 96-517), with amendments in 1984 (Public Law 98-620) to encourage cooperative relationships between universities and industry, with the goal of putting government-sponsored inventions in the marketplace. Burgeoning university-industry relationships have been attributed, in part, to patent policy (101).

On one hand, intellectual property rights stimulated and are critical to maintaining investment—public and private—in plant biotechnology research. Innovation must be protected and rewarded to realize a continuing flow of dollars to agri-biotechnology R&D (30,109). On the other hand, many individuals are concerned that increased patent activity is having serious and adverse consequences resulting in the "privatization" of agriculture (17,26,56). Greater awareness of potential profits to be accrued from patenting genes and products has led to a rush to register under the existing patent laws (30). Moreover, patenting in biotechnology is increasingly viewed as a defensive mechanism (42) to protect future investment and projects, rather than a means that expects immediate return.

To many in both the public and corporate sectors, increased patent activity is tying up, or has the potential to tie up, germplasm (28,30,44). Some argue that a noticeable slowing in the free exchange of germplasm that existed prior to patenting has occurred (28,44). In effect, they argue that the biological domain was once public domain, but has shifted to a private property right (27). Others argue that utility patents do not stifle free exchange (109). Rather than patents *per se*, recognition that germplasm is commercially valuable could be resulting in closer attention being given to free transfer (75). In any case, advances in both plant breeding and plant biotechnology require free-moving, international exchange of germplasm.

AGRICULTURAL BIOTECHNOLOGY RESEARCH FUNDING

The U.S. agricultural research enterprise is a system. Lodged partly in the private sector and partly in the public sector, it is comprised of a broad variety of institutions funding both traditional and biotechnological research in agriculture. In response to scientific, legal, economic, and political pressures, the system evolves, seeking to balance the diverse requirements and interests of each stakeholder. At issue is how research will be prioritized, what lines of research should be pursued, and what research roles are appropriate for the respective public and private sectors. This section examines who invests in plant biotechnological research in the United States and to what extent the funding source (e.g., Federal Government, public institutions, private corporation) influences the direction of agricultural research. (For a detailed accounting of biotechnology funding, see chs. 3, 4, and 5, and for agricultural funding in general [68].)

Public Investment

U.S. public investment in agricultural research involves two principal partners: the Federal Government and the States. Within the Federal sector, USDA funds the majority of plant research. In addition to the USDA, other Federal agencies, including the National Science Foundation (NSF), National Institutes of Health (NIH), Department of Energy (DOE), Agency for International Development, Department of Defense, and National Aeronautics and Space Administration, support basic science research on or applicable to plant biotechnology. NSF in particular, funds many basic research initiatives and training programs in the plant sciences. In the more recent past, NIH and DOE played critical roles funding basic plant researchers at non-land-grant institutions.

Funding for all agricultural research by the public sector is estimated at approximately $2.0 billion—$1.9 billion combined Federal and State support of the traditional USDA system and $100 million through grants from other agencies (68). Not all of this research, however, involves plants or biotechnology. The following sections describe plant research initiatives within the public sector and, where available, plant biotechnology applications. Targeted investment in education and training is also presented.

U.S. Department of Agriculture

A long tradition and a complex institutional funding structure characterize agricultural research investment by USDA. Most federally sponsored research in plant biology is conducted at land-grant institutions, which are part of a tripartite USDA complex that includes 72 land-grant institutions, 146 State agricultural experiment stations, and thousands of extension agents (one in virtually every county in the United States).

Determining the precise amount of USDA funding in plant *biotechnology* is problematic. Funding amounts for plant science or biotechnology projects are generally distinguished, but not both as a unit. Nevertheless, it appears that the majority of research funding obligated by USDA involves plant applications (103,105, 106).

USDA allocates research funds through the Agricultural Research Service (ARS) for intramural research, the Cooperative State Research Service (CSRS), and the Office of Grants and Program Systems for competitive grants funding. ARS sponsors in-house research allocated among 140 intramural research facilities located nationwide. CSRS distributes funds based on a formula incorporating each State's farm and rural population. CSRS-sponsored research is carried out largely at State agricultural experiment stations and colleges of veterinary medicine that are part of land-grant universities. CSRS funding includes a State-matching formula. Competitive grant funding by USDA was established nearly a century after initiation of the land-grant complex, and expenditures are not limited to land-grant institutions.

Within ARS, approximately 38 percent of research dollars (fiscal year 1986 appropriation of approximately $185 million) are specifically designated for plant science (106). The Competitive Research Grants Program of CSRS does break out plant biotechnology. Plant applications were 58 percent of funds for competitive grants awarded; biotechnology applications 45 percent; and plant biotechnology applications 28.5 percent (total budget $40.1 million) (105). Table 10-2 describes some of the kinds of projects funded by the CSRS competitive grants program.

In education and training, land-grant universities also support 80 percent of the Nation's plant biology faculty and graduate students (68). USDA funds 200 to 300 graduate students at both land-grant and non-land-grant institutions through training grants in four targeted areas, one of which is biotechnology (68). USDA also has a modest com-

Table 10-2.—Examples of USDA Competitive Grants Awarded for Plant Biotechnology

- Molecular Cloning of a Rubber Gene From Guayule
- Cloning of Maize Regulatory Genes
- Molecular Biology of Rice Genes
- Regulation of Soybean Seed Protein Gene Expression
- Organization and Manipulation of Wheat Storage Protein Genes
- Delivery of DNA Into Cells of Onion and Tobacco Using High Velocity Microprojectiles
- In Vitro Culture of Cool Season Forage Grasses
- Molecular and Genetic Studies in Barley
- Identification of DNA Markers for Disease and Pest Resistance in Potato
- Molecular Biochemistry of Herbicide Resistance
- Regulation of Cytochrome Synthesis in Photosynthesis
- Directed Mutation Studies of the Photosynthetic Cytochrome b6
- Regulation of Corn Nitrate Reductase: Application of Monoclonal Antibodies
- Regulation of Nitrite Reductase

SOURCE: U.S. Department of Agriculture, Office of Grants and Program Systems, Cooperative State Research Service, *Food and Agriculture Competitively Awarded Research and Education Grants, Fiscal Year 1986*, Washington, DC, 1987.

petitive postdoctoral fellowship program through ARS. Of the approximately 100 fellowships awarded in fiscal year 1986, about one-half were in biotechnology (68). CSRS funds Food and Agriculture Sciences National Needs Graduate Fellowship grants that supported 87 doctoral degree candidates (many in plant fields) in fiscal year 1986 (105).

National Science Foundation

NSF plays a pivotal role in funding basic plant biological research, training, and education. In fiscal year 1985, NSF awarded 50 percent of competitive Federal funding for plant research (71). In addition to research investment, agency expenditures are also devoted to developing the plant sciences human resource base. For example, NSF conducts a peer-reviewed, competitive postdoctoral plant biology fellowship program that emphasizes an interdisciplinary approach to expand an individual's training into plant biology—e.g., bacterial molecular biology to plant molecular biology. The program provides funds for approximately 20 fellows per year. NSF also sponsors a summer course in plant molecular biology for 16 scientists each year (68).

Science and Technology Centers for Plant Science

Plant biotechnology is one of several relevant research areas that could be covered at proposed multidisciplinary plant science research centers to be funded jointly by USDA, NSF, and the Department of Energy. The proposal initially will involve $10 million per year and use a competitive grant/peer review process to establish several centers with average annual funding of $1 to $2 million per center for 5 years. The Administration's Working Group on Plant Science believes that $250 million during the first five years of the program represents a realistic recognition that the scant amount of competitive funding for plant sciences needs to be increased or the search to elucidate many fundamental principles of plants will continue to lag (79). Collaborative arrangements (including funds, equipment, or people) between State and local governments, private foundations, and industries would be encouraged, although the grantee must be a doctorate granting institution with graduate programs related to plant sciences. Proposed centers are encouraged to form, wherever possible, research and training relationships with existing facilities, such as those of the Agricultural Research Service and National Laboratories (72).

States

States play a significant role in funding agricultural research, plant biotechnology included. One analysis reports that in 1985, the ratio of State to Federal appropriations through CSRS at State agricultural experiment stations was 3.5 to 1 (68); another estimates that the ratio is much less, approximately 2 to 1 (62). Total expenditures by State legislatures for State agricultural experiment stations approach $700 million annually (68). In addition to State contributions through CSRS, some States, such as Iowa, have targeted agri-biotechnology as a strategic industry for State investment (see box 10-B).

In addition to research and facilities funding, States have also recognized the importance of investing in human capital. For example, Iowa and North Carolina have special graduate and postgraduate fellowships in plant molecular biology.

Box 10-B.—Biotechnology in Iowa

"All encompassing" probably best characterizes the biotechnology effort underway in Iowa. Involving the State's executive and legislative branches, industries, and colleges and universities, the necessary components of a multi-faceted approach for success are each seemingly covered. These include:

- 2-year laboratory technician training,
- undergraduate biotechnology training,
- graduate biotechnology training,
- faculty development and recruitment,
- equipment acquisition,
- facilities improvement and new construction,
- tax incentives for industry R&D, and
- programs for employee training.

These efforts are targeted primarily toward agriculture, the State's principal industry.

Several State initiatives help ensure the availability of adequate personnel. In response to the needs of companies, a 2-year laboratory technician training program has been designed at Iowa Valley Community College. The program focuses on developing human capital skilled in recombinant DNA and monoclonal antibody technologies (39). The corporate-sponsored Undergraduate Agricultural Biotechnology Scholarship Program at Iowa State University (ISU) provides up to full-tuition scholarships for students. In 1984, the University of Iowa (UI) established the Iowa Biotechnology Training Program, funded by a competitive grant from the USDA (39). The program leads to a Ph.D. in microbiology or immunology (16). UI is also home to the Biocatalysis Research Group, an endowed graduate program (M.S., Ph.D.) that focuses on biocatalysis and bioprocessing (39,82). Finally, UI also awards degrees in chemical and materials engineering with an emphasis in biochemical engineering and biotechnology (110). The program provides coursework and research opportunities at the B.S., M.S., and Ph.D. levels (110).

In addition to student initiatives, faculty support has been enhanced. For example, at ISU a $1 million Pioneer Hi-Bred International Endowed Chair in Molecular Biology of Maize was established. A $400,000 grant awarded to ISU by the Northwest Area Foundation in 1984 allowed the creation of two new faculty positions in the genetics department (51).

Support for biotechnology extends beyond the universities to the State's government officials. The Iowa legislature has committed $18 million to Iowa State University for agricultural biotechnology research over the next 4 years (39). A half million dollars from State lottery funds were earmarked in fiscal year 1986 for biotechnology training, and $3.75 million in fiscal year 1987 for research funding (39). The legislature and governor have also supported building and equipment funding for ISU and UI (9,40,41,85,86).

Local and international businesses, such as Darst/Imperial Chemical Industries and Pioneer Hi-Bred International, play central roles in Iowa's biotechnology push—funding projects at the universities and interacting with government to optimize the State's biotechnology climate. Iowa offers a property tax abatement for businesses that expand their research activities, and the Iowa Jobs Training Program, developed in 1983, pays up to 50 percent of employees' salaries and as much as 100 percent of instructors' salaries for up to a year. Funds can also be used for specialized employee training worldwide. Companies that expand their work force by at least 10 percent, or those starting a new enterprise using the state training program, are eligible for a State income tax credit of more than $700 for each new employee (39).

The State's efforts to highlight its biotechnology industry are innovative and global. In Fall 1987, the State's Department of Economic Development, UI, and ISU sponsored a "Biotech Express Dinner Train" from Ames to Iowa City. Designed to highlight Iowa's biotechnology industry, State officials invited 300 American and 300 Japanese business executives for the 3-day affair (9).

It is too early to evaluate the overall success of Iowa's efforts. It is clear, however, that the concerted and intensive biotechnology initiatives underway are impressive, but no more so than the high-yield expectations. In his 1987 "State of the State" speech, Governor Terry Branstad stated, "Biotechnology will change the world, giving us new tools in crop and livestock production and processing. For a $35 million investment, Iowa State University officials are confident we will attract over $120 million in research to Iowa over the next decade . . . . They [the State's universities] are poised to help Iowa lead the nation in moving . . . to the age of . . . biotechnology" (11).

SOURCE: Office of Technology Assessment, 1988.

State universities outside the land-grant complex also are pivotal to research and training in plant biotechnology.

Combining matching funds and novel initiatives, **the bulk of State investment in biotechnology is probably related to plant agricultural applications**—at least 33 States have biotechnology initiatives (ch. 4), many with plant agriculture components (table 10-3).

Private Investment

Private funding for agricultural research derives primarily from industry, although private foundations, trade associations, and commodity organizations also channel money into the system. Companies also provide money to universities for doctoral and postdoctoral education and training.

Dollar expenditures for agricultural research by the private sector are difficult to determine. One recent survey places industry funding at approximately $2.1 billion (2), and it may approach $3 billion (101). Again, not all of this research involves plants or biotechnology, but, in the past few years, investment in plant research using genetic technologies has accelerated in both the private and public sectors (7). The following sections describe plant research and education investment by private sector interests, with particular focus, where available, on plant biotechnology.

Industry

Commercial funding of plant biotechnology research derives from two sources: large (often multinational) corporations and dedicated biotechnology companies (DBCs) (ch. 5). In a 1987 OTA survey of nearly 300 DBCs, 12.5 percent indicated plant agriculture as a primary or secondary focus. Corporate biotechnology companies (CBCs) involved in applications of biotechniques to plants are largely fully integrated seed companies. Research investment includes both intra- and extramural funding.

Table 10-3.—State-University Research Center Initiatives in Plant Biotechnology

State	Description
Georgia	State Legislature appropriated $7.5 million for the construction of a $32 million Center for Biotechnology at the University of Georgia. Research emphasis will focus on cattle, hogs, and peaches.
Indiana	Indiana Corporation for Science and Technology specifically targets biotechnology and agricultural genetics as 2 of 13 strategic areas. The Corporation has granted over $2.5 million for biotechnology projects at the Agrigenetics Center at Purdue University or the Molecular and Cellular Biology Center at Indiana University.
Iowa	State Legislature appropriated $18 million over four years to Iowa State University for agri-biotechnology research. See also box 10-B.
Maryland	Center for Advanced Research in Biotechnology established at the University of Maryland with agriculture as one of five research areas.
Michigan	Michigan Biotechnology Institute established at Michigan State University includes focus on plant genetic engineering and tissue culture projects related to forestry and new uses of agricultural surpluses.
Missouri	Food for the 21st Century Center established at the University of Missouri, Columbia.
New Jersey	Center for Advanced Food Technology established at Cook College, and the Center for Agricultural Molecular Biology established at Rutgers University.
New York	Biotechnology Institute created at Cornell University. New York State Science & Technology Foundation also has designated Cornell University a "Center for Advanced Technology." The agriculture and food industries are target areas of both programs.
North Carolina	North Carolina Biotechnology Center established, targeting agriculture and forestry as part of its R&D program. Center also offers graduate and post-graduate fellowships in plant molecular biology.
Ohio	Edison Animal Biotechnology Center established at Ohio University and the Biotechnology Institute at Ohio State University.
Oklahoma	21st Century Center under construction ($30 million) at Oklahoma State University, Stillwater. Focus of center will be agricultural biotechnology, water resources, and renewable energy.
Pennsylvania	Cooperative Program in Recombinant DNA Technology established at Pennsylvania State University. Penn State Biotechnology Institute established with agricultural biotechnology one targeted research area.
Washington	Washington Technology Center established. Projects funded include livestock, crop, and forestry applications of biotechnology.
Wisconsin	Biotechnology Center established at the University of Wisconsin, Madison includes a Plant Cell and Tissue Culture Service Facility. A high containment growth chamber for recombinant plants also is being developed.

SOURCE: Office of Technology Assessment, 1988.

Industry also recognizes the importance of supporting the manpower base for the plant sciences. For example, several companies, such as Ciba-Geigy, have established in-house postdoctoral training programs. Graduate and postgraduate students have benefited from Agrigenetics' investment at several university laboratories.

Philanthropic

Noncorporate private sources, including foundations, trade associations, and commodity organizations, invest in some agri-biotechnology research. The nature of the funded projects varies with the interest and purpose of the organization. Although the money usually supports research, funds are sometimes earmarked for training and education. For example, in 1982, the McKnight Foundation of Minneapolis announced plans to spend $2 million a year for the next 10 years on basic research and graduate education in plant biology. Most of that money is targeted for about a half dozen universities, with interdisciplinary research teams focusing on plant genetics. Grants will consist of up to $300,000 a year for the support of doctoral and postdoctoral research. An additional ten grants of $35,000 per year for 3-year periods will be awarded to university scientists conducting basic research in plant biology related to agriculture. Despite such efforts, philanthropic investment is modest compared to the funds available from public sources.

Collaborative Arrangements

The typology and purposes of collaborative arrangements (see ch. 7) in plant agricultural biotechnology apparently do not differ from other sectors. Industry interaction with land-grant institutions has a long tradition within the agricultural sector (23,78), although the number of formal collaborations between agricultural biotechnology companies averages one to two per company in contrast to seven or more for the human therapeutics sector (8).

Today, collaborative arrangements in plant agricultural biotechnology include university-government, university-industry, and university-industry-government associations. For example, State-university cooperation in agri-biotechnology has been manifest in the establishment of several research centers with plant biotechnology components (table 10-3). In addition to government-university interactions, several dedicated and corporate agri-biotechnology companies make grants or other arrangements with university researchers or research groups. Table 10-4 lists some types of projects that companies have funded, or presently fund, at universities. An ambitious consortium involving collaboration between universities, industry, and Federal and State Governments recently has been inaugurated (see box 10-C). Finally, a cooperative project, the Biotechnology Research and Development Corp., involving the USDA, several companies, the State of Illinois, and the Peoria Economic Development Council was recently formed (10).

Impact of Funding Source on Agricultural Research Investment

Historically, public investment in agricultural research has been through the land-grant system. Land-grant institutions were established on a public service basis different from that of other universities, with a tradition of an implied social contract to make its discoveries freely available to the public (101). Since 1965, however, federally funded agricultural research through formula funds and USDA has remained stagnant or declined (in constant dollars), while State and private sector support for agricultural research has increased significantly in real terms. Private sector investment now exceeds public funding. And, within the public sector, the funding structure is evolving. Has the changing funding mix influenced agricultural research investment?

Formula-based Funding v. Competitive Grant Funding

As mentioned earlier, charges have been leveled that the USDA research enterprise has not been at the cutting edge of science. Such criticism often focuses on the tradition of formula funding. In response, a competitive grants program has been established by USDA (93). The peer-reviewed, competitive grants program allows non-land-grant universities to participate in research thrusts funded by USDA. Peer review at ARS was recently

Table 10-4.—Types of Private Plant Agriculture Grants to Universities

Funding Source	University	Project Description
Agrigenetics Corp.	Cornell	Tomato hybridization through cell culture
Asgrow Seed Co. (Upjohn)	Purdue	Soybean research
Busch Agricultural Resources, Inc.	U. Arkansas	Rice breeding, genetics, and evaluation
Chocolate Manufacturers Assn.	Purdue	In vitro production of cocoa
Cotton, Inc.	U. Arkansas	Development of types of early maturing cotton for Eastern Arkansas
Crow's Hybrid Corn Co.	Cornell	Tissue culture regeneration
Dow Chemical	Purdue	Soybean plant regulation
Eli Lilly & Co.	Purdue	Wheat genetics research
Hershey Foods	Penn. State	Molecular biology of the cocoa plant
Monsanto	Rockefeller U.	Regulation of plant genes involved in photosynthesis
Nestle	Cornell	Bitterness in squash
North American Plant Breeders	Purdue	Evaluation of alfalfa and red clover varieties
Northrup King (Sandoz)	Cornell	Tissue culture regeneration
Pioneer Hi-Bred	Penn. State	Regulation of grain yield in maize
Popcorn Institute	Purdue	Improvement of popcorn hybrids
Quaker Oats	Purdue	Improvement of competitive ability of oats in Indiana and other Midwestern States
Rohm & Haas	U. Penn.	Support for Plant Science Institute
Showalter Trust	Purdue	Development of tissue culture systems to produce plant secondary products
Standard Oil	U. Illinois	Long-range improvement of food production, primarily in corn and soybeans
Upjohn	Purdue	Muskmelon breeding program

SOURCE: Office of Technology Assessment, 1988.

reviewed, and recommendations were made to strengthen the process in several ways (69).

The move to a competitive agricultural research program has led to concern that elite, well-staffed institutions will be favored. Critics charge that the peer review system that is generally used has resulted in the top 20 research universities receiving the bulk of Federal research dollars year after year (92). Under the grant process at the National Institutes of Health, critics point out 1 to 2 percent of institutions receive as much as 20 percent of the funding. With geographical considerations such an important part of the agricultural research sector, concern has been and continues to be expressed that the valuable research functions performed by the smaller land-grant institutions would increasingly receive less attention.

While sensitive to such concerns, others maintain that allocation of new and even redirected resources from USDA should be based primarily on competitive peer and merit review. They argue that such a system ensures that public dollars are invested most wisely and efficiently without limiting the character and diversity of U.S. agricultural research (68,93). These individuals contend that while there appears to be a threat to the system, the long-term impact will be beneficial, leading to a more competitive science and a more competitive industry (74).

Because competitive grants represent, at present, less than 5 percent of the USDA agricultural research budget, it is difficult to assess their impact, both on concerns raised and expectations held.

Box 10-C.—The Midwest Plant Biotechnology Consortium

The Midwest Plant Biotechnology Consortium (MPBC) is the first, and operationally most advanced, university-government-industry consortium to focus on agricultural applications of biotechnology. MPBC represents 15 midwestern universities, three Federal laboratories, 37 agribusiness corporations headquartered in the Midwest, and research institutes from eight States: Illinois, Indiana, Iowa, Michigan, Minnesota, Missouri, Ohio, and Wisconsin (29). While formally not participants in the MPBC, the Department of Energy, USDA, National Science Foundation, and National Institutes of Health have expressed interest in the technical, organizational, and economic purposes of the consortium (29).

The purposes of the MPBC are two-fold: to carry out basic research in plant biotechnology and to promote the transfer of that technology to foster economic competitiveness of U.S. agriculture and agribusiness. The issues and needs addressed by the MPBC encompass midwestern crops and cropping practices, particularly in the areas of plant growth, plant storage, pesticides and herbicides, processing, and seeds. Much of the basic research, however, on plants like corn and soybeans is relevant to other species (29).

Operating on the premise that a planned, coordinated basic research program on the biochemistry, physiology, molecular biology, and biophysics of plants—fields of interest to area universities and Federal facilities—can make major contributions to commercial biotechnology, the participating nonindustry members collaborated to prepare research preproposals in response to identified needs. The industrial participants of the MPBC then reviewed the preproposals and selected those with highest industrial relevance. The preproposals have been developed into full proposals, and are undergoing scientific peer review by individuals outside the Midwest and the MPBC (29). After completion of the review process, those with greatest technical merit will be submitted as the MPBC proposal to the USDA competitive grant process for Federal start-up funding (29).

The industry members of the MPBC have provided the initial cash for the consortium's policy and operating secretariat. Federal and State matching dollars are expected to fund the MPBC, with State funding used only for institutions within the State. Funds would be used primarily for training and support of students, fellows, and technical staff, not facilities or capital equipment. After five operating years, the entire project will be reviewed and continued only if its purpose of providing a fundamental research base to facilitate technology transfer is being met (29).

An important aspect of the MPBC is recognition that the basic knowledge foundation of plant biology necessary for commercial breakthroughs to new biotechnological products is lacking, and that this type of research funding is most appropriately provided by the Federal Government (29). Any intellectual property rights resulting from such research will reside with the research participants, as governed by the individual's institutional practices. Industrial members of the MPBC, however, would have access to the first disclosure of information, with further development pursued between the interested parties (29).

The MPBC is a rather unique collaborative effort in biotechnology, and certainly in plant biotechnology. Although the MPBC is organizationally one of the more advanced consortium endeavors, it is still embryonic. And while participants are optimistic about a prosperous future, antitrust obstacles must still be overcome (29). Nevertheless, the concept of enhancing U.S. competitiveness in agriculture, agribusiness, and biotechnology through a university-government-industry collaborative arrangement shows promise.

SOURCE: Office of Technology Assessment, 1988.

Increased Commercial Involvement

Agribusiness in the United States today is changing—becoming bigger, and also more horizontally and vertically integrated (101). Historically, corporate research programs are driven by the economic incentive to produce a profit-yielding product. In the case of plant biotechnology, however, private investment in basic research was necessary to enhance the paucity of knowledge available about plant systems. This increased spending by the commercial sector was coupled with real dollar declines in Federal support (28).

Some believe that an overall weakening of the public sector role in agricultural research, especially within the land-grant complex, and a corollary strengthening of the position and interests of the private sector is occurring, and that this could portend problems. For example, strengthening support by the private sector could present problems in intellectual property or developing technology of real benefit for farmers (62). Arguments also have been raised that an erosion of the public interest in agricultural research might not be in the best interests of the Nation if high-cost/high-yield projects are pursued, rather than low-input/low-cost options (28).

In addition to the increased money being spent by industry, a recent flurry of merger activity involving agribusiness has also raised questions about the direction of agricultural research investment. Since the late 1960s, seed companies increasingly have become subsidiaries of larger corporations, especially chemical firms. Some express concern that consolidation of seed and agrichemical companies will make projects such as herbicide-resistant plants attractive, and that such applications will lead to increased dependence on chemicals also produced by the same firm.

Others point out that private investment in agri-biotechnology is vital to the country's economic well-being and will enhance the global position of American agriculture in the world marketplace through low-input options. It is also argued that the opportunities afforded by private involvement in agri-biotechnology could produce health and environmental benefits through industrial efforts to develop products that decrease the present dependence on chemical pesticides and herbicides and lead to more efficient nonchemical control methods.

Private spending on agri-biotechnology cannot, however, replace public involvement. Private support for basic research, intramural and extramural, is expected to decline (95) as companies increasingly identify potential products and shift funding toward applied R&D. Industry can, however, act as an advocate for public funding of agri-biotechnology research (68) as it looks to public investment for advances in fundamental research. Because universities are well-springs of innovation, commercial agriculture will benefit from collaborative arrangements that support basic research. (Questions surrounding such collaborative arrangements are discussed in ch. 7.)

Resource Allocation Within USDA

Public investment in agricultural research is necessary because incentives for private research are often inadequate. The social return could be considerable, but private profit is meager, with gains captured by other firms, by producers, and by consumers (84).

Implied in public funding of agricultural research is responsibility to the public, which is entitled to broad benefits. For example, historically Black colleges of agriculture in the land-grant system have important programs targeted to smaller farms. Yet today, the USDA-led enterprise is increasingly challenged by consumers, environmentalists, farmworkers, and rural development advocates who have a range of concerns and research priorities. Concern about land-grant accountability led to a lawsuit in California examining the role and impact of federally funded research. In November 1987, a verdict, which is being appealed, was issued ordering the University of California to develop a process to ensure that Federal Hatch Act appropriations are used to enhance rural life and promote small family farms (13).

Over its long history, public research has demonstrated that it contributes to the maintenance or enhancement of a competitive structure in the agricultural production, farm supply, and marketing sectors (84). Concerns recently have been raised, however, that the U.S. public agricultural research system lacks focus toward equity for farmers and consumers, and that an examination of priorities could be necessary (26).

USDA's Users Advisory Board has recommended that public sector research should encourage strategies that increase profitability, reduce the need for subsidies, protect the environment, and enhance rural development and world competitiveness (106). With or without biotechnology, public sector agricultural research institutions could emphasize biological processes and cultural management in the field, new crop diversification, and host-based disease and insect resistance for crops. Most agree—in both the commercial and public interest sectors—that **U.S. agricultural research programs need to be revitalized and recredited in the public's mind. This issue is paramount if the USDA system is to reap maximum benefit.**

COMMERCIALIZATION OF AGRICULTURAL RESEARCH

The United States' ability to transfer technology—including agricultural technology—from laboratory to marketplace is under increasing scrutiny. Generic issues described earlier also apply to commercialization of plant agricultural biotechnology as well (see chs. 5 and 6). For example, collaborative arrangements have been designed to enhance commercialization of plant biotechnology research. What is the general profile of commercial plant agricultural biotechnology, and what issues are important to product development in this sector?

As mentioned earlier, about one-eighth of DBCs (37 companies) surveyed by OTA in 1987 are involved in R&D of plant agricultural applications. The OTA survey also found that the profile of patent activity for these companies was similar to that for DBCs in general (see chs. 5 and 6). **Including corporate participants, the commercial sector for plant agricultural biotechnology does not appear to have changed appreciably since a 1984 OTA report of industry activity** (94).

Nevertheless, expectations for profitable returns on investment in agri-biotechnology are high. Estimated revenues from world seed sales range from $30 to $60 billion (6,7), with the U.S. share representing approximately one-fourth the world market (7). Some analysts predict that, with genetically modified seeds, the world market could reach $150 to $180 billion by 1990 (6), and that disease-, pesticide-, and herbicide-resistant plants could constitute a sizable portion of the $10 billion agricultural chemical market (6). Others are less optimistic, but still see real growth, anticipating a slow to moderate growth rate (5 percent annually) over the next decade (7). This represents a doubling between 1982 and 1995 (7). Yet, compared to human therapeutics, raising adequate capital for research has been relatively difficult for most agricultural biotechnology companies, including plant biotechnology firms (76). However, the world-wide nature of agriculture could result in biotechnological agriculture processes and products, both plant and animal, becoming the largest sector in the industry (64,65). Table 10-5 lists one analysis of probable years of commercialization for several genetically manipulated crop plants.

To achieve success under either growth pattern, widespread commercialization of plant biotechnology will require breakthroughs in several technical areas. It will also depend on other factors, including environmental regulation, university-industry relations, economic incentives, and consumer acceptance. A comprehensive analysis of the commercial plant biotechnology sector is beyond the scope of this chapter. As a case study, however, two issues specific to commercialization in the plant biotechnology sector merit discussion: institutional barriers to development and personnel needs.

Table 10-5.—Probable Year of Commercialization for Some Genetically Manipulated Crop Plants

Tomatoes	1988
Other vegetables	1989
Potatoes	1989
Sugar cane	1989
Fruit	1990
Rapeseed	1991
Rice	1991
Sunflower	1991
Alfalfa	1992
Barley	1992
Corn	1992
Sorghum	1992
Soybeans	1992
Wheat	1992

SOURCE: M. Ratafia and T. Purinton, "World Agricultural Markets," *Bio/Technology* 6:280-281, 1988.

Institutional Barriers to Development

Practical use (through public or commercial availability) of plant agricultural research is ingrained in the fabric of the U.S. system. Although this chapter focuses primarily on aspects that affect investment in U.S. agri-biotechnology research, it is also important to delineate parameters that influence the flow of plant biotechnology products to the open market. The following three sections analyze three parameters identified and examined at a 1987 OTA workshop (95), that are impeding or could impede rapid plant biotechnology development: the existing knowledge base, regulation, and property rights.

Knowledge Base

While an enormous information base has provided a substructure for sweeping advances in biomedical science (68), **similar basic knowledge about plants and plant systems is in short supply.** Experts from academia and industry nearly all agree that **the sparse fundamental knowledge base underlying plant agricultural biotechnology, especially in crop species, is the rate-limiting barrier to commercial development,** and that developing the base is critical to future U.S. efforts (95).

The level of basic scientific knowledge about plants is rudimentary and limited to certain species (89). Basic biochemistry of plants and plant systems is poorly understood. For example, the metabolic basis of drought resistance is not understood, let alone the genetics of this trait. The same holds true for many plant traits. Knowledge about gene expression and developmental regulation of plants is not well defined, and while plants are a major source of pharmaceuticals and other specialty chemicals (45,94,99), biotechnological applications are poorly exploited; only one product is currently under production (45,87). At the plant molecular level, only a few important plant genes have been cloned and sequenced (67), and complete molecular maps to correspond to genetic maps are available for only two or three species (36,42).

A comprehensive treatise on the knowledge gaps in plant sciences is beyond the scope of this chapter, however, table 10-6 lists some basic research needs in plant biotechnology. A following section analyzes the division of labor between the public and private research sectors to meet these needs.

Table 10-6.—Some Knowledge Gaps in Plant Agriculture Needing Basic Research

- Gene, seed, embryo libraries and banks
- Model systems to correlate with important crop species
- Metabolic regulation and expression of polygenic traits
- Germination: storage, differentiation, and properties of embryonic tissue
- Plant differentiation: morphology and physiology for all stages
- Gene structure and function
- Biochemistry and mechanisms of plant regulators and hormones

SOURCE: Office of Technology Assessment, 1988.

Regulatory Uncertainty

Government regulates commerce for a wide range of reasons, including protection of human health and the environment. State initiatives and the Federal regulatory structure for biotechnological products were analyzed in a previous OTA report (96). Does the present regulatory environment act as an institutional barrier to commercial development of plant biotechnology?

Regulatory uncertainty stands as the second major barrier to commercialization of agricultural research (95), **and could become the most serious** (28,36,42,47,78). For the agricultural sector of the biotechnology industries in particular, regulatory delays have hampered the movement of products from laboratories and greenhouses, to small-scale, experimental field tests (20). While the furor appears greater when the application involves micro-organisms, genetically engineered plants with bacterial or fungal genes also have been tied up in the regulatory system (20,96).

Routine progress toward field and environmental testing of genetically engineered organisms has been slow, with controversy and confusion among Federal regulatory agencies leading to uncertainty within the biotechnology research community and industry (68). This uncertainty has resulted in significant delays in field research on potential agricultural biotechnology products (68). Dissatisfaction with Federal regulation of biotechnology (both too much and too little) has focused on the two agencies that regulate agricultural products: USDA and EPA (20).

From a commercial standpoint, Federal regulation needs to be affordable and should support, not stifle, technology development (36). Unanticipated regulatory delay can dramatically affect the profitability of products and the commercial agricultural biotechnology research agenda (47). Regulatory uncertainty, for example, affects decisions by companies on whether to spend $1 to $2 million on greenhouses only because of concern over future field tests v. greenhouse work, instead of investing the money in research (42).

In contrast to regulatory delay for pharmaceutical biotechnology, crop agriculture is particularly sensitive to a time lapse. A one-month delay at a critical time can result in a lost year of development. A one-year delay can reduce profit by 50 percent during the product lifetime and stem cash flow (47). **Missing a seasonal planting window for an experimental field trial of a plant biotechnology product represents a major risk to be factored by companies into the R&D process, with such factoring affecting, and probably reducing, total investment decisions.** Diverting funds away from R&D could be especially critical to the survival of smaller DBCs which, unlike corporate seed suppliers, do not have seed revenues to offset short-term losses.

In some respects, regulation could be less an institutional barrier itself than a consequence of the barrier just discussed—poor knowledge base. Only further research can alleviate this lack and reverse the regulatory uncertainty it creates.

Property Rights

As discussed earlier, proprietary protection is critical to maintaining investment in research, especially commercially sponsored research. High costs for R&D and regulatory approval of products favor patenting because a company wants to protect its investment. Are there intellectual property issues that are barriers to developing plant agricultural research?

The structure of the plant protection system does not seem to be a barrier to commercial development (36,78), but rather an idiosyncracy adding complexity to management of plant intellectual property. Some sentiment exists that patent and related issues are overblown (36,78), especially compared to regulatory issues (36). Choosing the type of protection to seek is characterized as a basic business decision (36). For example, there are advantages and disadvantages of securing protection of sexually and asexually reproduced plant varieties by obtaining a utility patent through 35 U.S.C. §101 rather than PPA or PVPA. Utility patents for plants provide somewhat greater protection (49,60) and lower nominal cost (60), and the holder of a utility patent can exclude others from using the patented variety to develop new varieties. A Certificate of Plant Variety Protection, however, affords 18 years of protection, whereas the life of a utility patent is 17 years. In the case of many agriculture companies, especially large firms, formal protection is not generally a part of their corporate milieu; rather they rely on trade secrets (ch. 6).

Although the domestic structure of plant intellectual property probably does not hinder commercialization, a lack of international harmony for plant protection is a potential barrier, especially considering the global economy in which the agricultural sector operates (31,36,47,78). Additionally, calls for patent extension for agri-biotechnology products (similar to the situation for pharmaceuticals) have been made. In light of the present regulatory uncertainty just described, some parties believe patent extension, based on the period a product is under regulatory review, would compensate companies and stimulate them to undertake higher risk research ventures. Analyses of international patent issues, how a type of protection is chosen by a company, and patent term extension will be analyzed in a forthcoming report on *New Developments in Biotechnology: Patenting Life*.

Personnel Needs

Adequate numbers of trained personnel in a variety of disciplines are necessary for successful commercialization of U.S. plant agricultural biotechnology, and the demand remains substantially unmet (5,68). A 1985 survey found that companies seeking plant scientists cited shortages in plant molecular biologists who had solid education and training in plant science (as opposed to individuals who cross over from animal or microbial systems), plant tissue culture experts, and plant geneticists or breeders with expertise with in vitro technologies (50). In other words, industry cited shortages in just about every area. These personnel shortages are not limited to the private sector, since industry draws its talent from universities. What measures could solve this problem?

The Federal role in funding education and training is crucial. Industry support—at universities or private institutions and in-house programs—is also important. Equally important is adequate research funding. Personnel needs are self-driven; if enough money is available to support research, then individuals will be drawn to the field. **Research funding drives the process, ensuring an adequate supply of trained personnel for universities, government, and industry.**

THE FUTURE OF AGRICULTURAL RESEARCH

The U.S. agricultural research enterprise is an evolving system. In addition to the three impacts just described, the changing global market for agricultural products affected and continues to affect agri-biotechnology research. In the late 1970s and early 1980s, the goal of increasing agricultural production drove public policy and the agricultural research agendas of both the public and private sectors. Today, however, the goal of U.S. agricultural research is increasingly focused on farming profitability.

In a recent survey, most Americans said that research into genetic engineering should be continued (98). Americans support and encourage a range of agri-biotechnology applications, such as disease-resistant crops, frost-resistant crops, and more effective pesticides (98). Given this popular support and these high expectations, what is the long-term outlook for U.S. investment in plant biotechnology research?

Increased Federal attention to agricultural research seems to be the most urgent need. In 1939, approximately 80 percent of federally sponsored research was for agriculture, while in 1985, agricultural research comprised less than 2 percent of Federal research expenditures. USDA, the largest Federal sponsor, is allocated only 5.2 percent of total Federal research funds, and only 1.4 percent of USDA's budget is used for research. Given the potential return on investment in agricultural research, the present spending pattern might be too low for priority research areas that have the ability to enhance and ensure the future competitiveness and profitability of U.S. agriculture (83). In particular, more fundamental research on plant applications is needed than on animal applications, because basic knowledge about plants is less (68). While recognizing the present climate of fiscal restraint, both public and private interests express the conviction that funding should be reallocated from other activities to agriculture, not reallocated within agriculture (95). Furthermore, increased integration between the basic biological sciences and applied agricultural research is paramount.

Agri-biotechnology research performed in the private sector has different long-term objectives from public sector research. What is the proper division of labor between the diverse interests? Balance needs to be found between molecular biology and traditional breeding, private and public interests, and applied and basic research. While recent research agendas and interests of each sector have overlapped rather extensively, the public sector can no longer rely on the private sector to perform substantial basic research. The private sector, troubled by public sector usurpation, must also recognize the traditional responsibilities and constraints (including the broad and specific "public good" mandate) of the public sector. Applied research is an important component of the public agricultural research tradition—necessary to fill gaps left by industry, explore novel applications, and keep the government abreast of developments in the field. Accordingly, **to strike and maintain a balance, agri-biotechnology research performed by both sectors will need careful management so that its research benefits the public and enhances the competitiveness of the U.S. agricultural industry.**

At present, scientific, legal, economic, and political forces have seemingly converged to accelerate the rate of evolution and the direction of U.S. agricultural R&D. Yet change in the system is not novel, and adopting a siege mentality would be counterproductive (90). Serious new issues have been raised, but the embryonic nature of the agricultural biotechnology industry complicates the assessment of long-term effects. Continued examination and private and public support for long-range planning seem prudent.

ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

Three policy issues related specifically to applications of biotechnology to plant agriculture were identified during the course of this study. The first concerns possible congressional actions regarding research funding. The second involves regulating products of plant biotechnology, and the third concerns the impact of intellectual property protection of plants on germplasm exchange.

Associated with each policy issue are several options for congressional action. The options are not, for the most part, mutually exclusive, nor is the order in which the options are presented indicative of their priority.

ISSUE 1: Is Federal funding of research in plant biotechnology adequate?

Option 1.1: Take no action.

Congress could conclude that current Federal spending for plant agricultural research is adequate. Continuing the present level of funding, however, could result in a static agricultural sector that is unable to respond to future economic, technological, and scientific needs—both domestic and international. Knowledge in the plant sciences would continue to remain in short supply, limiting commercialization even further.

If Federal spending remains the same, the reduced role for public research could result in a slower rate of technological progress.

Option 1.2: Increase spending.

Congress could determine that present spending for agricultural research is insufficient. If Congress increases agricultural research funding, U.S. preeminence in this sector would probably continue. Increased expenditures for training would ensure an adequate supply of personnel for both universities and industry.

Option 1.3: Decrease spending.

The U.S. agricultural sector has added a surplus to the U.S. trade account every year since 1960. Underlying this success has been research support—with an annual rate of return for investment in agricultural research in the range of 33 to 66 percent.

If Congress determines that Federal investment in plant biotechnology is excessive, it could decrease allocations for this sector. Decreased funding for agricultural research would result in diminished returns that would undermine the agricultural economy.

Option 1.4: Reallocate existing resources.

Should Congress conclude that present funding levels are adequate or, because of fiscal constraints, must remain the same, then it could direct that Federal resources be reallocated.

Congress could increase the Competitive Grants Program at USDA at the expense of formula funding for land-grant institutions. Increasing dollars for peer-reviewed, competitive-based grants could be an effective mechanism to ensure that Federal investment in basic research is being well spent. However, historically, the nature of federally sponsored agricultural research has been applied. This fact, combined with a decentralized structure that includes local agricultural experiment stations and extension services, provides a unique national capacity to identify and solve local or regional problems. Reallocating resources away from formula-based funding would diminish the important role that even the smallest, poorest funded land-grant universities play.

Likewise, Congress could decrease spending for competitive grants within USDA or other agencies, such as NSF. In general, competitive research funding is directed toward basic research. Because the database for plant sciences is sparse, decreasing awards that foster excellence in this area could hinder rapid progress in plant biotechnology.

Option 1.5: Direct increases in State funding at State Agricultural Experiment Stations through the Cooperative State Research Service.

To increase total spending or offset Federal reductions, Congress could require States to increase their contributions to agricultural research through the Cooperative State Research Service at State Agricultural Experiment Stations. If increased State spending were to result in an overall increase for agricultural research, then continued development should occur.

ISSUE 2: Agricultural applications of biotechnology will increase significantly over the next several years. Is the statutory and regulatory structure governing environmental applications of plant biotechnology adequate?

Option 2.1: Take no action.

Congress could take no action if it determines that the present regulatory structure provides adequate review to ensure environmental safety and public health, or that experience with the existing structure has been insufficient to ascertain its adequacy.

If Congress takes no action, the Coordinated Framework for the Regulation of Biotechnology (51 F.R. 23301) will continue to direct regulation of plant biotechnological products.

Option 2.2: Direct the Office of Science and Technology Policy (OSTP) to report on the implementation of the Coordinated Framework.

Congress could direct OSTP to evaluate, or specifically commission an independent analysis of, the process by which plant agricultural applications have been handled by regulatory authorities. A comprehensive review of the timeliness and efficiency of regulatory review, resolution of competing agency jurisdictions, scientific knowledge gained through field testing, actions of State and local regulation, community involvement, and consequences of field testing on environmental safety and public health could demonstrate whether the present regulatory framework best serves all interested parties.

Option 2.3: Relax regulatory constraints.

If regulatory requirements are judged excessive, Congress could direct executive authorities to relax regulations. The existing USDA regulatory authority for plant biotechnology includes the Federal Plant Pest Act (7 U.S.C. 150aa-150jj), the Plant Quarantine Act (7 U.S.C. 151-164, 166, 167), the Federal Noxious Weed Act (7 U.S.C. 2801 *et seq.*), the Federal Seed Act (7 U.S.C. 551 *et seq.*), and the Plant Variety Protection Act (7 U.S.C. 2321 *et seq.*) (51 F.R. 23339). Modifications that remove restrictions would make regulations for some applications more consistent with the regulation of nonengineered cultivars.

Less stringent regulation of environmental applications of genetically engineered plants might decrease costs associated with experimental field testing and increase investment in research. However, if planned introductions in the future (in contrast with those now contemplated or likely) define new risks, then reevaluating relaxed regulatory requirements could be necessary.

Option 2.4: Preempt State and local regulation of agricultural applications of biotechnology.

Increased State and local interest in regulating biotechnology exists. If Federal regulation of biotechnology is deemed adequate, Congress could enact a statute that preempts State and local regulation on this issue.

Uniform authority could remove some present regulatory uncertainty, streamline the process, and decrease delays in field testing. If Congress preempts such regulation, however, local concerns might receive less attention. Federal preemption could also hinder cooperative regulatory efforts between Federal and State agencies that are presently in place, e.g. the Animal Plant Health Inspection Service's regulation of genetically engineered organisms or products under the Plant Pest Act.

Option 2.5: Direct the Secretary of Agriculture to report how USDA is complying with National Environmental Policy Act requirements (NEPA) in its regulation of genetically engineered plants.

The statutory mission of USDA is to assist the development of agriculture and husbandry in the United States. NEPA requires all Federal agencies to consider the environmental impact of activities funded with Federal dollars.

If Congress determines that a conflict between NEPA requirements and the statutory responsibilities of USDA exists, then Congress could amend the mission of USDA to explicitly include environmental protection.

ISSUE 3: Does intellectual property protection of plants in the United States ensure adequate germplasm exchange?

Option 3.1: Take no action.

Congress could conclude that the present intellectual property structure for plant protection does not interfere with germplasm exchange. If Congress takes no action, inventors would continue to seek protection through the avenue they deem most appropriate or advantageous. Germplasm exchange would continue on an ad hoc basis.

Option 3.2: Direct the Secretary of Agriculture to report on the impact that plant protection has on germplasm exchange.

Congress could direct the Secretary of Agriculture to report on the impact that proprietary interests in plants has on germplasm exchange. To date, any information on the issue is anecdotal. Because all interested parties agree that free exchange of germplasm is necessary to continue progress in plant biotechnology, a comprehensive analysis examining trends in plant protection and germplasm exchange could reveal that a problem exists, that no problem exists, or could direct attention to potential problems.

SUMMARY AND CONCLUSIONS

The largest industry in the United States, agriculture is one of the most efficient and productive sectors in the country's economy. Agriculture contributes to approximately 20 percent of the gross national product, and employs more than 1 in 5 Americans. Increasingly, however, problems beset the U.S. agricultural economy. Research alone cannot solve all of the problems, but can significantly alleviate them if resources are available. Historically, the returns on Federal R&D in this sector have been high, so efforts to provide relief through agricultural research could yield powerful results.

Both public and private sector agricultural research endeavors are in a state of flux. Several factors have converged to affect U.S. investment decisions in such research, including the discovery of the new biotechniques, intellectual property rights and plants, and the funding source for plant agricultural biotechnology research.

Biotechnological innovation in plants spans a spectrum of applications. New techniques and new uses continue to arise. The new technologies can potentially accelerate the rate, precision, reliability, and scope of improvements beyond that possible through traditional plant breeding, while also reducing costs. Some have expressed concern, however, that biotechnology has led to private sector-, proprietary-dominated research efforts. Others point out that biotechnology has afforded unique contributions to agricultural research and created positive economic effects. Biotechnology's effect on the balance of manpower between traditional plant breeders and molecular geneticists is seemingly reaching equilibrium.

Plant property developments have influenced agri-biotechnology research profoundly. Intellectual property protection of plants has stimulated interest and investment in plant research. However, increased plant protection activities have led to concerns about free-flowing exchange of germplasm. Such exchange is necessary to continued advances in plant breeding and biotechnology.

The U.S. agricultural research enterprise is lodged partly in the public sector and partly in the private sector. Each has different agendas and purposes. Understandably, the perceptions of proper roles, research priorities, and investment decisions clash. The issue of balance—formula funding v. competitive grants, private v. public, basic v. applied, traditional plant breeding v. molecular biology—seems foremost. Spending patterns by the public sector should be responsible and sensitive to broad public benefit. Industry can serve as an advocate for public agri-biotechnology research and as a funding source for research to enhance U.S. competitiveness. Adequate research funding also pulls in interested and qualified manpower to the agricultural research system.

The commercial profile of the plant agricultural sector does not appear to have changed appreciably since an earlier OTA report. Achieving widespread success, however, will require expansion of the plant science knowledge base. Lack of fundamental knowledge about plants and plant systems is probably the rate-limiting barrier to complete commercialization of plant biotechnology research. Regulatory uncertainty stands as the second major barrier and looms as potentially the most serious. Crop agriculture is particularly sensitive to regulatory delay—a one month lapse can result in a company missing the planting season and, thus, an entire year of development. In some measure, regulation itself could be less an institutional barrier than one arising from a poor fundamental knowledge base. Intellectual property issues do not appear to hinder commercialization, although patent term extension to compensate for regulatory delays might stimulate companies to undertake higher risk ventures.

Increased Federal and popular attention to agricultural research seems to be the most urgent need. Given the potential return for agricultural research, the present level of expenditures might be too low to ensure the preeminent role that guarantees U.S. agriculture vitality and profitability. While recognizing the present climate of fiscal restraint, proposals to reallocate already scarce agricultural resources to meet unmet needs disturb both commercial and public interests. In particular, USDA funding for fundamental research on plants is required to a greater extent than animal basic research. Furthermore, increased integration between the basic biological sciences and applied agricultural research is paramount.

As scientific, legal, economic, and political forces continue to direct U.S. investment in agricultural research, including plant biotechnology, ongoing examination and long-range planning seem prudent.

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Chapter 11

U.S. Investment in Biotechnology Applied To Hazardous Waste Management

"The prospect of controlling pollution is one of the reliable rhetorical war-horses trotted out by advocates of the new biological technology every time someone asks what this new baby might be good for."

Douglas McCormick
Bio/Technology
May 1985

"If it wasn't for the high cost of the alternative, this (bioremediation) wouldn't be worth considering at all."

Perry L. McCarty
Stanford University
July 1987

"Burning and burying are no solution. They just make less of a bigger problem."

Ananda M. Chakrabarty
University of Illinois
September 1987

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Chapter 11

U.S. Investment in Biotechnology Applied to Hazardous Waste Management

INTRODUCTION

Destroying persistent toxic waste is frequently touted as a major benefit of new biotechnologies. Natural microbial populations have a wide range of waste management capabilities, from degrading hydrocarbons to accumulating cadmium. While existing micro-organisms can degrade most natural chemicals, organisms frequently require some assistance to be effective against many manmade chemicals. Many applications of biotechnology for hazardous waste management are still experimental, and the investment in developing biotechnology for waste treatment and cleanup is small when compared with efforts in pharmaceuticals or agriculture. **Current applications rely on conventional techniques of genetic manipulation and microbiology; the use of recombinant DNA to develop microbes with special capabilities for waste degradation has been limited.**

Research and development in biological waste treatment methods is growing and may equal R&D efforts in thermal technologies. Companies using biological cleanup techniques have attracted substantial amounts of venture capital in recent years.

In this chapter, biotechnology for hazardous waste management refers to all efforts to engineer systems that use biological processes to degrade, detoxify, or accumulate contaminants. These systems can use naturally occurring or laboratory-altered microbes or both. Genetic engineering refers specifically to the use of recombinant DNA techniques but does not include more conventional, less precise techniques of altering genes, such as random mutation and selection.

This chapter briefly decribes the science underlying biotechnology for hazardous waste management and looks at some of the private and public sector activities in researching, developing, and applying new knowledge in biology to treat hazardous waste. The state of scientific knowledge and the barriers to further development of the field are analyzed.

This chapter focuses on issues specific to applying biotechnology to waste management, although some issues are generic to innovative waste treatment technologies. OTA has addressed many issues involved in waste management and waste reduction in its reports, *Technologies and Management Strategies for Hazardous Waste Control* (93) *Protecting the Nation's Groundwater From Contamination* (90), *Superfund Strategy* (92), *Serious Reduction of Hazardous Waste* (91), *Ocean Incineration: Its Role in Managing Hazardous Waste* (89), *Wastes in Marine Environments* (94), and *From Pollution to Prevention: A Progress Report on Waste Reduction* (88). Two related OTA studies are in progress: *Municipal Solid Waste Management* and *Superfund Implementation.*

THE CONTEXT FOR RESEARCH

Several factors make the development of new technologies for waste management environmentally important and economically attractive. In 1985, U.S. industry generated at least 569 million metric tons of hazardous waste, according to EPA (103). Most hazardous waste has been put in unlined surface dumps, with no barrier between the waste and groundwater (54). The Federal Government has spent more than $2 billion on the cleanup of closed or abandoned waste sites, and industry has spent hundreds of millions more in complying with new Federal and State regulations on hazardous waste management (54). The Congress has strongly expressed its desire for hazardous waste generators to move away from land disposal and to use permanent treatment methods. These views are reflected in the Hazardous and Solid Waste Amendments (HSWA, Public Law 98-616) of 1984 and the Superfund Amendments and Reauthorization Act (SARA, Public Law 99-499) of 1986.

Waste cleanup is a substantial and growing industry. The cost of waste disposal is expected to increase significantly in coming years. OTA has estimated that it will cost $300 billion over the next 50 years to clean up waste already generated (92). Gross annual costs of both solid and hazardous waste disposal have risen from $827 million in 1976 to $2.4 billion in 1984 (54). Arthur D. Little projected an $8 billion market for commercial hazardous waste treatment and disposal services by 1990, and the market could top $13 billion by 1995 (30).

Regulatory Pressures

Regulation both drives and constrains waste management practices. Within the last two decades the Federal Government has established regulatory and research programs to control and develop waste disposal activities. In addition to HSWA and SARA, the laws most pertinent to waste cleanup and disposal are the Toxic Substances Control Act (TSCA, Public Law 94-469), the Resources Conservation and Recovery Act (RCRA, Public Law 94-580), and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, Public Law 96-510).

In 1976, Congress passed the Toxic Substances Control Act to address comprehensively the risks of hazardous chemicals. The Act gives EPA highly flexible powers to control "an unreasonable risk of injury to health of the environment," including the control of disposal methods (2).

Also in 1976, Congress passed the Resources Conservation and Recovery Act to cope with disposal of hazardous waste as it was generated. This program called for "cradle to grave" control of all hazardous waste and requires permits for treatment, storage, and disposal facilities.

RCRA was amended by the Hazardous and Solid Waste Amendments of 1984, which established deadlines for banning land disposal of many hazardous and persistent wastes. HSWA also required that all land disposal facilities monitor groundwater and certify financial responsibility by November of 1985. Fewer than one third of the 1,650 land disposal facilities certified compliance; the rest closed (53).

HSWA also greatly expanded EPA's authority to require corrective action for releases of hazardous wastes at RCRA facilities, where EPA has ultimate authority over what cleanup technologies are used. Therefore, if the agency develops the necessary knowledge base in biotechnology, it is possible that EPA would begin to recommend microbial degradation for RCRA corrective actions (109).

In 1980, Congress responded to rising public concern about hazardous waste sites with the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA or "Superfund"). Superfund requires the generator, transporter, and disposer of waste to bear the burden of cleaning up existing nonconforming disposal sites. The EPA has responsibility for monitoring and implementing cleanup at these sites. Superfund was originally funded for 5 years at $1.6 billion. The law was reauthorized in 1986 at $8.5 billion by the Superfund Amendments and Reauthorization Act (SARA, Public Law 99-499).

Among the important provisions of the new law are deadlines for initiating cleanup actions; cleanup standards that emphasize permanent remedies; a program to accelerate cleanup at Federally owned hazardous waste sites; and broad new research and development authorities (73). In authorizing SARA, Congress mandated that the President shall "utilize permanent solutions and alternative treatment technologies or resource recovery technologies to the maximum extent practicable" (Public Law 99-499).

Thus, the regulatory environment is increasing pressure on waste generators to reduce waste and to find permanent solutions to the waste that is generated. Over the past 2 years, regulations have banned the land disposal of solvents and other wastes. The Land Disposal Restrictions of HSWA stipulate that, by 1990, all RCRA hazardous wastes must meet certain treatment standards before they can be land disposed. Small-quantity waste generators, previously exempt, must now comply with regulations. In addition, SARA directs EPA to choose permanent remedies when possible, rather than burying wastes.

Economic Pressures

Regulations have and will continue to increase the cost of waste disposal, making alternative technologies more economically feasible. EPA reported that design and construction standards for RCRA-approved landfills raised the price of land disposal from as little as $10 to $15 per metric ton in the early 1970s to $240 per metric ton in 1986 (98). According to another report, prices charged by commercial waste management firms increased 30 to 400 percent in 1985 alone (99).

These price increases, moreover, predate the enactment of most provisions of the Hazardous and Solid Waste Amendments of 1984 (HSWA). HSWA requirements have already resulted in the closure of some 1,100 noncompliant land disposal facilities. If implemented as enacted, HSWA will force most land disposal facilities to install liners and leachate collection systems and will prohibit land disposal of wastes for which alternative treatment methods exist (54).

EPA estimates that the HSWA will add at least $2.25 billion to industry's annual cost of waste disposal, approximately doubling 1984 disposal costs (54), although this estimate does not reflect potential savings from waste reduction and lower-cost on-site disposal.

Companies with new technologies and services for waste management are seeing sales increase at 20 to 30 percent per year (52). Stock prices of six waste companies followed by Kidder Peabody & Co. rose substantially higher than Standard and Poor's 500-stock index from 1984 until the October 1987 stock market crash and have rebounded strongly from the crash (46).

SCIENTIFIC BASE OF BIOTECHNOLOGY FOR WASTE MANAGEMENT

The rationale for using micro-organisms to degrade pollutants comes from experience with nature. Micro-organisms, particularly bacteria, have a variety of capabilities that can be exploited for waste management and disposal and have been intentionally used for municipal waste management for over a century.

A large proportion of organic compounds of biological and chemical origin are biodegraded, predominantly by micro-organisms (69). Organic compounds of biological origin are readily degraded. Many different micro-organisms are known to degrade oil (19). Industrial chemicals that are similar in structure to natural compounds are frequently also biodegraded.

Persistent Chemicals

Persistent compounds, however, have chemical structures not found in natural compounds and so resist degradation by most naturally occurring micro-organisms. Such compounds are called *xenobiotics*. In addition to xenobiotics, other compounds may persist in the environment, because the compounds are present in too dispersed or too toxic a concentration, the organisms necessary for degradation are absent or occur in low amounts, one organism cannot degrade the compounds completely, or the oxygen and nutrients necessary for degradation are lacking.

Industrial chemicals have been present in the environment for "only an instant in evolutionary time" (69), a period that is often not long enough for the evolution of the necessary catabolic enzymes, the molecules made by organisms to bring about degradative reactions. Micro-organisms, however, display "a striking plasticity" to evolve the necessary capabilities and, on occasion, to do so in a short amount of time (83) and sometimes evolve new pathways rapidly when confronted

Table 11-1.—State of Knowledge of Biodegradation of Common Pollutants[a]

Pollutant	Organism degrades or transforms	Pathway known	Enzymes characterized	Genes sequenced	RecDNA technology	On-site biodegradation underway
Acetone	⊕	⊖	⊙	⊙	⊙	⊙
Aluminum and Compounds	⊙	⊙	⊙	⊙	⊙	⊙
Anthracene	⊕	⊕	⊖	⊙	⊙	⊕
Arsenic	⊕	⊕	⊙	⊙	⊙	⊙
Barium	⊙	⊙	⊙	⊙	⊙	⊙
Benzene	⊕	⊕	⊕	⊖	⊖	⊕
Benzo (a) Pyrene	⊕	⊖	⊙	⊙	⊕	⊕
Bis (2-Ethylbenzyl) Phthalate	⊕	⊖	⊙	⊙	⊙	⊙
Cadmium (Cd)	⊖	⊕	⊕	⊙	⊕	⊙
Carbon Tetrachloride	⊕	⊖	⊖	⊙	⊙	⊙
Chlordane	⊖	⊖	⊖	⊙	⊕	⊙
Chlorobenzene	⊕	⊕	⊖	⊖	⊖	⊙
Chloroform	⊕	⊕	⊙	⊙	⊙	⊙
Chromium	⊖	⊙	⊖	⊖	⊖	⊙
Chromium, Hexavalent	⊕	⊖	⊙	⊙	⊙	⊙
Copper and Compounds (Cu)	⊙	⊙	⊙	⊙	⊙	⊙
Cyanides (soluble salts)	⊕	⊕	⊖	⊙	⊙	⊕
DDT	⊕	⊕	⊖	⊙	⊕	⊙
Dichloroethane	⊕	⊖	⊙	⊙	⊕	⊙
1,1-Dichloroethane	⊕	⊖	⊙	⊙	⊙	⊙
1,2-Dichloroethane	⊕	⊖	⊙	⊙	⊙	⊙
1,1-Dichloroethene	⊕	⊖	⊙	⊙	⊙	⊙
Ethylbenzene	⊕	⊕	⊖	⊖	⊙	⊙
Iron and Compounds	⊕	⊙	⊙	⊙	⊙	⊙
Lead (Pb)	⊖	⊖	⊙	⊙	⊙	⊙
Lindane	⊕	⊖	⊙	⊙	⊕	⊙
Manganese and Compounds (Mn)	⊕	⊙	⊙	⊙	⊙	⊙
Mercury	⊕	⊕	⊕	⊕	⊕	⊕
Methyl Ethyl Ketone	⊕	⊖	⊙	⊙	⊙	⊙
Methylene Chloride	⊕	⊕	⊙	⊙	⊙	⊙
Naphthalene	⊕	⊕	⊖	⊖	⊕	⊕
Nickel and Compounds (Ni)	⊕	⊖	⊖	⊙	⊕	⊙
Pentachlorophenol (PCP)	⊕	⊕	⊖	⊙	⊕	⊕
Phenanthrene	⊕	⊕	⊖	⊖	⊙	⊕
Phenol	⊕	⊕	⊖	⊖	⊙	⊕
Polychlorinated Biphenyls (PCBs)	⊕	⊕	⊖	⊖	⊖	⊕
Pyrene	⊕	⊖	⊙	⊙	⊕	⊕
Selinium	⊕	⊙	⊙	⊙	⊙	⊕
1,1,2,2-Tetrachloroethane	⊕	⊕	⊙	⊙	⊙	⊙
1,1,2,2-Tetrachloroethene	⊕	⊕	⊙	⊙	⊕	⊙
Toluene	⊕	⊕	⊕	⊖	⊖	⊕
1,2-Trans-Dichloroethylene	⊕	⊖	⊙	⊙	⊙	⊙
1,1,1-Trichloroethane	⊕	⊕	⊕	⊕	⊕	⊙
1,1,2-Trichloroethane	⊕	⊖	⊙	⊙	⊙	⊙
Trichloroethylene (TCE)	⊕	⊖	⊖	⊙	⊕	⊕
Vinyl chloride	⊕	⊖	⊙	⊙	⊙	⊙
Waste Oils/Sludges	⊕	⊙	⊙	⊙	⊙	⊕
Xylenes	⊕	⊕	⊙	⊙	⊖	⊕
Zinc and Compounds (Zn)	⊖	⊙	⊖	⊖	⊖	⊙

KEY: ⊕ – Known
⊖ – Partially Known
⊙ – Not Known

[a] This table was compiled from information provided to OTA by 20 researchers in the field of biodegradation. Some compounds listed include multiple congenors, for which organisms may be known that degrade some congenors but not others.

SOURCE: Office of Technology Assessment, 1988.

with significant concentrations of xenobiotics in their environment.

Micro-organisms have been identified that degrade at least 42 pollutants commonly found at hazardous waste sites targeted for cleanup on the National Priority List (NPL) sites (table 11-1). Current research is aimed at exploiting the natural degradative capabilities of microbes to accelerate degradation, enable the organisms to live in new environments, and attack new contaminants.

Simple Bioremediation

Waste management biotechnology typically involves mixing live organisms or their products with the waste to degrade or transform it. Biological treatment requires that an organism live in a sometimes exceedingly hostile environment. In nature, certain organisms live in extreme environments. Thus, in some cases, it has been possible to isolate micro-organisms from a particular environment (where they have been environmentally selected) and introduce them into similarly contaminated sites. Alternatively, supplying the required nutrients and conditions may allow organisms already present to degrade waste. Isolated organisms may also be further adapted in the laboratory with mutagenizing agents (e.g., radiation) or with selective pressure (see figure 1). Many bacteria have such short generation times that under strong selective pressure a year is more than enough time to evolve desired characteristics. Under the right laboratory conditions, many bacteria can divide about every two hours (or faster), creating over 4,000 generations per year. Such a large number of generations provides significant opportunity for evolution (51).

In these cases, almost nothing may be known about the biochemistry or the genetics of the organism that breaks down the pollutant. Lacking comprehensive biodegradation and physiological information, strategies to enhance degradation involve reseeding the site with bacteria as they die out (bioaugmentation) or enhancing the site with nutrients or oxygen required by the micro-organisms for optimum growth and performance (bioenrichment). For simple waste sites involving readily degraded contaminants, such as fuel oils, these strategies suffice.

Remediation of Complex Sites

Waste sites pose significant challenges to organisms. Waste sites can involve materials in any form: solid, liquid, gas, or mixed. Waste sites can involve a single material, a family of related compounds called *congeners,* or a mix of unrelated wastes. Pollutants in lagoons or landfills may leach into the groundwater. Pollutants may occur highly diluted, highly concentrated, or in locally concentrated "hot spots" (13).

Different environments require different strategies. Immobilized enzymes in a bioreactor may be the best method to treat a waste stream at the source. As complexity grows, a single organism may not be able to survive or compete in the contaminated environment. To clean up an ecosystem, an ecosystem-level approach may be required, incorporating a variety of organisms (49) (see figure 11-2).

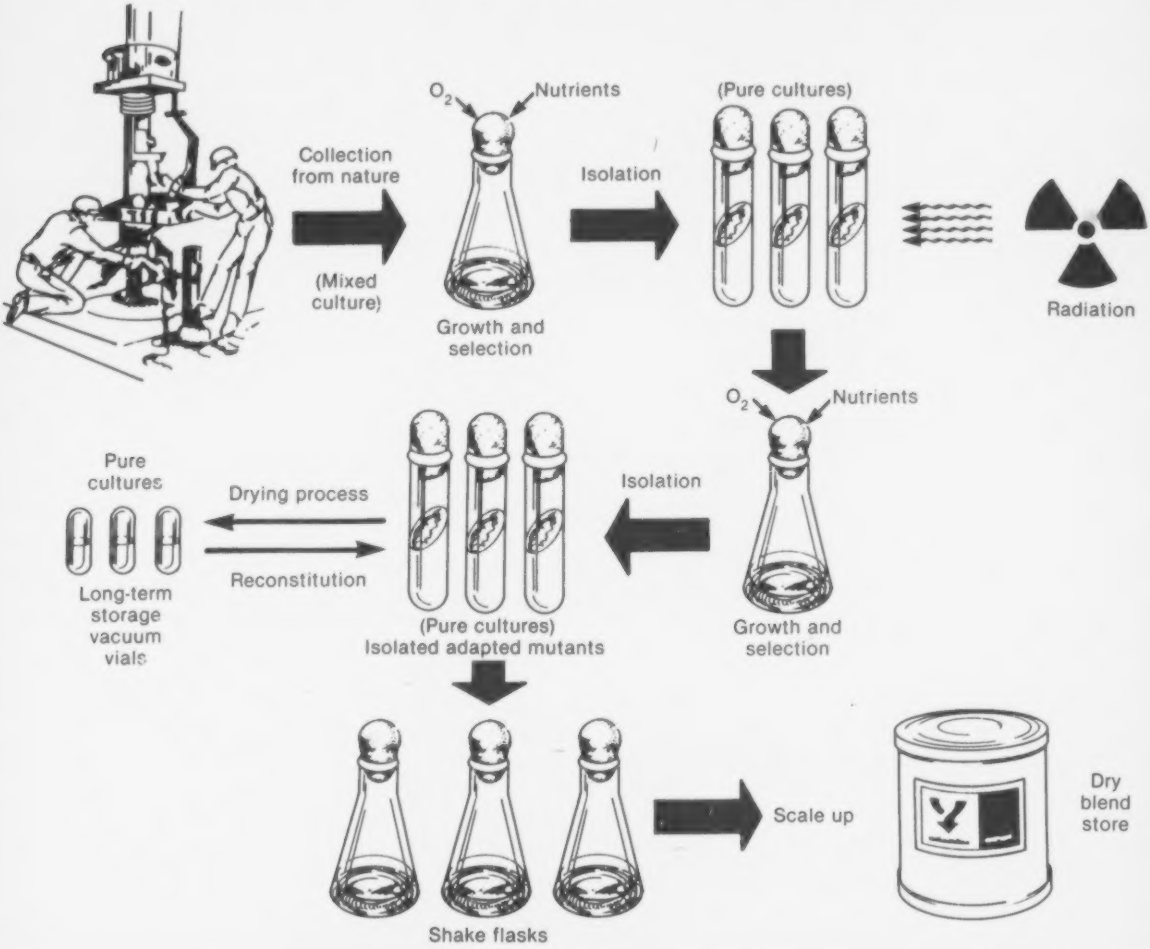
Environmental conditions affect organism function. Although an organism can degrade or otherwise change a toxic chemical, it might do so only at certain concentrations or at a relatively slow rate. Mixtures of chemicals at sites might poison the organism, or the degradation reaction might supplant other necessary reactions, such as energy production. Many organisms require oxygen, which might not be available in the site. Finally, many pollutants occur attached to particles or in other physical states that can make them unavailable to the organism (76).

Finally, degradation itself may be the limiting factor in the use of biological systems for site remediation. If the waste provides the sole carbon source for the organism, then as the waste is depleted, the food supply for the organism is also depleted. The organism may or may not survive as the waste reaches lower concentrations. Thus, full remediation may not be achieved.

Modern Biological Strategies

The term degradation generally indicates that a product is changed, but not necessarily the extent to which it is altered or broken down. Many demonstrations of degradation rely on evidence that a single compound is lost, without determining whether new products are formed (76). Degra-

Figure 11-1.—Laboratory Selection and Enhancement of Micro-organisms


Collection from nature
(Mixed culture)
O_2
Nutrients
Growth and selection
Isolation
(Pure cultures)
Radiation
O_2
Nutrients
Growth and selection
Isolation
(Pure cultures)
Isolated adapted mutants
Drying process
Reconstitution
Pure cultures
Long-term storage vacuum vials
Shake flasks
Scale up
Dry blend store

Micro-organisms indigenous to various environmental sites can be isolated and screened for degradative capabilities. This figure shows how naturally occurring organisms can be selected in the laboratory and, if desired, subjected to mutagenizing agents such as radiation. This imprecise method can sometimes produce new strains of organisms with enhanced capabilities.

SOURCE: Polybac Corp.

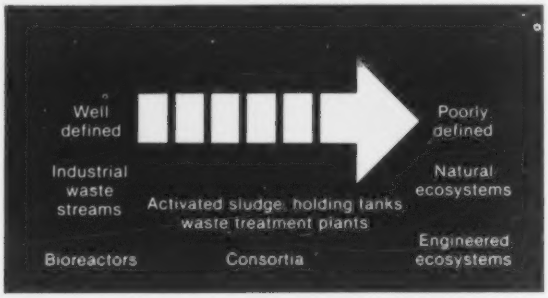
dation can produce new toxic products (76). Simply defined, true biodegradation is the metabolism of a compound to innocuous products (35). It is therefore necessary to identify the pathways of degradation and define the acceptable products and amounts.

With better knowledge of microbial genetics, microbial physiology, and microbial ecology, scientists and engineers can develop more efficient strategies for biodegradation.

Ideally, a complete biological strategy for research and development to degrade a pollutant would include:

- finding and characterizing an appropriate organism with degradative capabilities;
- defining the conditions that allow the micro-organism to exist and function;
- defining the pathway of metabolism for the pollutant and for any other related or critical cell products;

Figure 11-2.—The Continuum of Environments in Xenobiotic Degradation



THE CONTINUUM OF ENVIRONMENTS IN XENOBIOTIC DEGRADATION: A wide variety of environments means that in order to eliminate toxic materials a variety of strategies must be employed. In waste streams from process plants an immobilized enzyme in a bioreactor may prove sufficient. As complexity grows a single organism may not be able to survive or compete in the contaminated environment. In order to clean up ecosystems an ecosystem level approach may have to be undertaken, incorporating a variety of organisms and trophic levels.

SOURCE: Wayne G. Landis, Chemical Research, Development and Engineering Center, Aberdeen Proving Grounds, MD.

- identifying and characterizing the enzymes of the pathways; and
- characterizing the treatment environment.

If genetic engineering is applied, these additional steps are necessary:

- locating the genes for the enzymes and the control of the pathways; and
- manipulating the genes to improve degradation rates, stability, or substrate range.

In some applications, sequencing the genes of interest may provide some clues for ways to alter gene products to degrade persistent compounds.

Metabolic Pathway Design

Three approaches are being used in the laboratory to design beneficial metabolic pathways (the first two are more commonly used):

- *chemostats* and other laboratory systems, in which organisms are grown under long-term selective conditions to encourage the organisms to metabolize new substrates;
- *in vivo genetic transfers*, in which the gene of a useful enzyme from one organism is recruited into a pathway of another organism via natural genetic processes; and
- *recombinant DNA technology*, in which genes are introduced by in vitro techniques into a new host to create a new pathway.

Recombinant DNA technology enables the most precise manipulation of genes, but also requires extensive background knowledge and thus research and development. Selective pressure and in vivo transfer can often be accomplished without extensive basic research. In certain cases, the waste site itself has provided selective pressure to generate organisms capable of metabolizing new substrates, such as the decades of exposure to creosote and pentachlorophenol (PCP) waste.

EPA and University of Illinois scientists have used the in vivo transfer strategy to further modify a strain of *Pseudomonas* isolated from a chemostat. The transformed *Pseudomonas* can completely degrade 2,4,5-T, one of the active ingredients of Agent Orange. This strain carries a plasmid (an extrachromosomal unit of DNA) with the genes responsible for making one or more enzymes that degrade the compound. Modifying the plasmid so that it can be introduced and maintained in a range of host organisms that can exist in toxic sites could lead to environmental application (37).

Genetic Enhancement of Organisms

One strategy uses recombinant DNA technology to rationally design pathways that can degrade xenobiotic compounds. These pathways can be constructed in two ways: restructuring existing pathways or assembling entirely new pathways from enzymes or portions of enzymes (37). The latter strategy is called patchwork assembly.

Many perceive the benefits of using, wherever possible, natural pathways in indigenous organisms while using recombinant DNA technology to develop reactions for recalcitrant compounds. Work is progressing on molecular biological approaches to several classes of recalcitrant compounds. For example, a pathway is known that degrades DDT, one of the most persistent pesticides in the environment, to DCB, an acceptable product (76). However, one step in the pathway requires oxygen. Eliminating the oxygen requirement would be advantageous in many applications. Basic research in recombinant technology is needed to develop organisms that will work without oxygen (34,58,61,81).

Other laboratories are working on genetic approaches to facilitate the removal of toxic forms of metals, which pollute various waste streams and soils. This process can reclaim valuable metals (12,41,84,108).

Useful Microbial Properties

In some cases, the pathways, enzymes, and genes are known and available to degrade a pollutant, but the conditions in which the pollutant exists inhibit or kill the organisms. Such conditions include unusual concentrations of the pollutant, extreme temperatures, high salt concentrations, extreme pH, and the presence of additional chemicals that are toxic to the organism (76). Genetic approaches to these problems include increasing the activity of a gene so the organism can live in more toxic concentrations or placing the requisite genes in organisms that can exist in these extreme environments.

Linking genes for surfactants and emulsifiers with genes for degradation may permit organisms to work more effectively (21), since the physical state of the pollutant is often critical to degradation. Pollutants frequently occur in partially solid lagoons where the chemical adheres to soil (55, 76) or is mixed with oil.

The search for degradative activity has turned up two reactions with surprising and potentially broad applications. In one, the enzyme ligninase degrades lignin, a naturally occurring compound that resists degradation by most micro-organisms. The enzyme has been reported to partially degrade PCBs, dioxin, lindane, PCP, and DDT (11, 15,116). For practical applications, low concentration of the pollutant is a problem as the enzyme may attack other materials in the site rather than the target pollutant.

In the other a newly discovered anaerobic reaction breaks the chlorine-carbon bond in aromatic compounds—one of the most recalcitrant chemical bonds and a major stumbling block in the destruction of wastes. Removing the chlorine is a key step in degrading PCBs, chlorinated benzenes, chlorinated phenols, and dioxins (76). This recently discovered anaerobe, isolated from sewage sludge, removes the chlorine from chlorobenzoate, producing benzoate. While chlorobenzoate is not a major pollutant, it serves as a model for major pollutants (29). Recently, this dechlorination reaction has been shown to work on hexachlorobenzenes and some PCBs (33).

Microbial Physiology and Ecology

Research and development in microbial physiology and ecology are much less developed than microbial biochemistry and genetics. These aspects have serious implications for the use of organisms in the environment to reduce waste and pollution.[1] Only 1 to 10 percent of all soil organisms are known or cultured (22). Even for known microbes, little is known about the entire set of reactions that occur in any one organism or how these reactions are interrelated and controlled. Even less is known about the relationship of an organism to its environment and to other organisms. Knowledge of physiology and ecology is especially important in nutrient enrichment and bioaugmentation. Otherwise, the efficiency and the outcome of the biosystem cannot be known.

Microbial Communities

Micro-organisms are not isolated in the environment but occur in mixed microbial communities. Microbial communities are sometimes able to degrade pollutants that a single organism could not. If the conditions are right, a series of reactions can be accomplished by the community of organisms. For example, the dechlorination reaction described previously is followed by at least two other reactions carried out by other specialist organisms, one that transforms benzoate into acetate, hydrogen, and carbon dioxide, and another that converts hydrogen and carbon dioxide into methane (29).

In another case, enrichment by an analog chemical, a chemical similar in structure to the pollutant but without the chlorine attached, causes the requisite bacteria to grow and induces degradation. Then other organisms, which have not yet been isolated, metabolize the products. Creating new genotypes that would work in concert with the indigenous organisms could replace the analog chemical. At least one laboratory is exploring this strategy (34). Providing oxygen and nutrients increases the cost of treatment substantially, both in the cost of the raw material and in the cost of supplying and mixing in the additives. Reducing the need for additives would produce significant savings.

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[1] A more thorough discussion of microbial ecology and other aspects of the environmental application of novel organisms can be found in OTA's report, *Field-Testing Engineered Organisms: Genetic and Ecological Issues (87).*

Exploring Other Organisms

One approach to reducing the need for additives is to use anaerobes, which do not require oxygen. Anaerobes might also be capable of novel reactions. Basic knowledge of most anaerobes is lacking, and genetic engineering of anaerobes is problematic. Researchers are, however, beginning to systematically seek reactions in anaerobes that can be developed to efficiently degrade aromatic hydrocarbons in soil (34,47,58).

While most research in the past has focused on bacteria, other organisms also perform desired reactions, such as fungi (15,38), algae (74,88), protozoa (50), yeast (107), clams (50), and plants (7,41).

Site Engineering

Biotechnology waste treatment sites provide significant and unique challenges to environmental engineers. The site engineer must ensure that the organism degrades the pollutant, treating the contaminant directly where it occurs (in situ), using a contained bioreactor, or using a combination of these two. Nonbiological technologies, such as air stripping (the removal of volatile compounds via a jetstream) and incineration, may be used in conjunction with biological treatment.

Site engineers must consider at least five criteria:

- The availability of the contaminants. Getting micro-organisms into contact with sorbed or nonaqueous contaminants is often limiting for oils, some solvents, pesticides, dioxins, and PCBs (74).
- The ability of the degrading strains to live and function. The ecology of the treatment environment determines whether or not desired micro-organisms will survive and do their job (74).
- The ability to degrade pollutants at very low concentrations. Achieving the very low concentrations usually required for hazardous waste cleanup requires micro-organisms adapted to function at low concentrations or reactor conditions designed to allow very low concentrations (74).
- The ability to cope with a range of conditions, particularly unexpected substances and concentrations.
- The need for low costs. Cost-effective approaches to waste cleanup require designs to minimize costs of equipment, energy, and manpower. The cost of the organisms, once identified and developed, is relatively low. Cost-effectiveness requires reactor designs that minimize initial capital and operations costs (74).

Demonstration projects have shown that appropriate bacteria will metabolize pollutants in landfills if they are maintained with proper energy sources and nutrients in thin layers of well-prepared, hydrated soil. For soil pollutants, a technique called landfarming may be used (14,60,85). This involves establishing treatment domains, pretreating the soil for pH and other conditions, spraying the soil with the micro-organisms, and maintaining the site with the proper humidity, oxygen, and nutrients. Providing nutrients and oxygen and mixing the components properly are major tasks. In current applications, treatment has been confined to surface layers (1.5 to 6 feet) of soil (44,72,85).

Currently, data concerning the optimal ratios of micro-organisms and nutrients to pollutants are largely derived from laboratory trials. Scale-up on site is difficult (76). Field conditions can vary significantly, changing expected results.

Most waste sites present a variety of problems for in situ treatment. Frequently wastes are mixed and in extremely varied concentrations, making both assessment and treatment difficult (8,76). In lagoons, liquid pollutants may adhere to solids, significantly reducing reaction rates (55,56). La-

Photo credit: Ecova Corp.

Daily tilling of soil provides oxygen to naturally occurring microbes, enabling them to remediate hydrocarbon-contaminated soil in an enclosed, solid-phase soil treatment facility. Current applications of biotechnology to waste management rely on naturally occurring microbes; the application of genetic engineering to this field remains some years away.

goons frequently leak and the pollutants may be found in the unsaturated (vadose) zone or in the water-saturated (aquifer) zone, contaminating the groundwater.

Among the most difficult sites to clean up is groundwater that contains low molecular weight, semi-volatile substances, such as trichloroethene (TCE), a widely used industrial solvent. In these cases, in situ treatment means injecting materials to create a reaction site in the groundwater. Thus, the resulting products and the migration of contaminants must be well understood. In situ treatment of soil contamination, on the other hand, can increase groundwater contamination, at least temporarily, as contaminants are released from the soil. Then the degradation reaction can occur in the groundwater (65).

In order to better control the conditions of the reactions and circumvent some of the safety concerns related to in situ treatment, bioremediation companies often use contained bioreactors. Here the process is more analogous to fermentation or sewage treatment technologies, where the pollutant is passed through a closed or controlled system. Considerable research is underway to optimize such bioreactor systems. Promising techniques include the use of fixed films (10,67), fluidized beds (75), microbes immobilized on beads (25,36,62), and microbes immobilized by membranes (4).

Directly at the end of a waste stream, the pollutants may be known, consistent, relatively pure, and moderately concentrated. **Because of these factors, there is emerging interest in the use of biotechnology to treat an undesired prod-**

uct within the waste stream or directly at the end of the pipeline where the cost of collecting the material is less and the conditions may be better controlled (18,36,91,110,111). In some cases, biotechnology might be used for waste reduction. For example, the use of ligninase to pulp wood could reduce the air and water pollution of chemical pulping (42).

BIOTECHNOLOGY APPLICATIONS IN HAZARDOUS WASTE MANAGEMENT

The application of biotechnology to hazardous waste management is new and less developed than applications in the pharmaceutical or agricultural industries. The relative merits of conventional versus biotechnological approaches to waste management are currently being debated. **Questions regarding the effectiveness and economic attractiveness of biotechnological techniques for waste management have not been resolved.** Conventional methods, e.g., airstripping, incineration, and containment, have a longer history, are better understood, and are thus frequently preferred. Company representatives have reported difficulty obtaining permits for biological remediation techniques (26,86). Such difficulties are common for innovative treatment technologies.

In contrast, certain industries historically have used conventional biotechnology to use or treat waste, have matter-of-factly adopted limited innovations in the field, and are convinced of its economic advantage. In other cases, changes in the regulatory environment (such as California's recent ban on open airstripping of volatiles), poor economic projections of the conventional technologies, or reduced availability of dump sites have forced some industries to explore new technologies.

At least 65 companies are involved in some aspect of biotechnology for waste management (see app. D). Some of these companies are dedicated biotechnology companies (DBCs, see ch. 5), others are waste management companies, and some are waste generators. A few companies have fully functioning sites relying on micro-organisms or products of micro-organisms to detoxify waste. Other organizations are engaged in demonstration projects. Several independent and young companies dedicated to biotechnological waste treatment have emerged.

No waste management company is currently using or even testing genetically engineered micro-organisms in the environment, although research on genetic engineering of model organisms is proceeding in laboratories. Current, on-site biotechnology strategies in the waste industry involve the use of either environmentally selected organisms or laboratory adapted, crossed, or mutagenized strains. Biological approaches are frequently integrated with conventional approaches.

Current applications of biological degradation focus on fuel oils, common industrial solvents such as benzene, wood preservatives such as PCP and creosote, and other compounds that are relatively amenable to biodegradation. One company president expressed a commonly held feeling in saying that there is so much crude oil, benzene, and diesel oil spilled around the country that there is no need to look for more exotic applications (115).

Various cost savings are attributed to biodegradation systems over other methods, but generalizations are difficult to make due to the variability of waste sites. **While various claims of cost savings have been made, few if any demonstrations by disinterested parties, such as EPA or state environmental agencies, clearly evaluate the cost and effectiveness of biological cleanup compared with other cleanup technologies.**

Waste Stream Cleanup

Bethlehem Steel Company uses a conventional biological approach to handle the coke oven waste water at its Sparrows Point, MD, plant. The coke oven waste stream contains phenols, cyanides, and ammonia, comprising about 4,000 to 6,000 pounds per day of phenol. Prior to 1970, the waste was dumped directly into the Chesapeake Bay. Now the waste stream goes through the equivalent of a sewage treatment facility. This facility is seeded with sludge from local sewage that contains naturally acclimated microbes. The daily output of phenol is reduced to about 2 pounds (99.9 percent reduction), a level in compliance with the National Pollution Discharge Elimination System for discharge of water.

The Sparrows Point plant was used to set EPA's "Best Available Technology" standard. Economic evaluations from the 1970's showed that the biological treatment plant was less expensive to build than other methods at that time by $1.2 million and is simple and inexpensive to run ($1.7 million as compared with $2.6 million for the conventional treatment for one year in 1978). All but one other steel plant in the United States have adopted this treatment method, although recent changes in effluent standards, requiring treatment of ammonia, are again forcing a change in treatment technology. Bethlehem Steel had been examining the use of biological methods to degrade the petroleum hydrocarbons in steel rolling mill solid waste at a site in Bethlehem, PA, until poor economic conditions forced the company to cut back at all levels and terminate its program on biotechnology (80).

Wood Treatment Site Cleanup

Wood preservation plants have created a significant number of waste sites. Koppers Company, a diversified manufacturing company with interests in wood preservation plants, has created a subsidiary environmental services company, Keystone Environmental Resources, Inc., to deal with waste sites resulting from wood preservation plants. Keystone received EPA funds for a demonstration project to clean up a wood preservation site in Nashua, NH, that contained creosote, polynuclear aromatic hydrocarbons (PAHs), PCP, and dioxins in soil. The treatment system was established on a prepared bed of soil and loaded with a 1-foot layer of soil augmented with cow manure and fertilizer. The soil was sprayed periodically with water and tilled once a week to improve mixing and aeration (44). In 5 months of degradation, over 75 percent of PCP and over 95 percent of polynuclear aromatic hydrocarbons (PAHs) were degraded. Neither the groundwater nor the soil beneath the system were affected by the chemicals in the treatment system (86). The soil went from being visibly contaminated with oil and grease to the consistency of garden soil "which might be used for construction site fill" (44).

PCB Degradation

General Electric Corp. (GE) has extensive contamination problems resulting from the widespread use of polychlorinated biphenyls (PCBs) in electrical transformers beginning about 50 years ago (13). GE began examining the use of micro-organisms to biodegrade PCBs and other contaminants in 1981. In the laboratory, they isolated 35 to 40 mixed cultures; upon purification of two dozen of these cultures, several strains were found to degrade PCBs exceptionally well, and two of these showed novel pathways. The genes for PCB-degrading enzymes from one strain have been cloned. The first laboratory demonstration project treated soil spiked with PCBs; next, soil from a contaminated site was treated in the laboratory. As of September 1987, a site test was underway at South Glens Falls, NY, where oil containing PCB was used for dust control on a race track. GE provides its strains to other companies and academic laboratories. (85). None of these strains, however, degrades the more persistent highly chlorinated PCBs (82).

Chemical Manufacturing Wastes

The Occidental Chemical Corp. is responsible for a number of chemical dump sites, including Love Canal. Occidental, its subsidiary TreatTek, and BioTal (formerly BioTechnica Ltd.) have claimed full-scale remediation assisted by microbial technology at two sites.

The Hyde Park Landfill in Niagara, NY, was used from 1963 to 1975 as a disposal site for an estimated 73,000 metric tons of chemical waste, including phenols, halogenated organics, and halogenated aromatic compounds (especially chlorinated benzoic acids), including dioxin. A compacted clay cover was placed over the landfill in 1978, and a leachate collection system made of tile was installed around the perimeter in 1979. The leachate is collected in a sump, pumped into a lagoon, the lagoon allowed to settle, and the supernatant trucked to a nearby treatment plant. The conventional treatment uses activated carbon, at an estimated cost of $21 million over the next 10 years. The company developed batch bioreactors using organisms selected from contaminated sites, which reduce the need for activated carbon by 96 percent, saving an estimated $20 million at this site alone.

At an abandoned gasworks site in England, coal tars, phenols, cyanides, heavy metals, and other contaminants were similarly treated by traditional methods, supplemented by microbial methods, to reduce phenols from 500 to less than 100 mg/kg in 8 weeks. Full-scale treatment will require excavation to layer the soil (112,113,114).

Groundwater Treatment

At a Superfund site in California, Ecova Corp. operates a groundwater decontamination system that combines an air stripper with a bioreactor to remove chlorinated hydrocarbons and soluble organics. The air stripper is a 35-foot column that blows air at a cascade of groundwater, thus stripping volatile hydrocarbon molecules from the water. After removal of volatile organics, the groundwater is transferred to a bioreactor to degrade the soluble organics. The bioreactor is a 10,000-gallon tank seeded with microbes and a nutrient mix developed specifically to biodegrade the remaining soluble organic contaminants. The bioreactor contains an agitator to provide aeration and instrumentation to monitor contaminant levels and rates of degradation. The treated groundwater meets standards established by the California Regional Water Quality Control Board (chlorinated hydrocarbons of 5 ppb and soluble organics of 1 ppm), and the effluent can be discharged to the public sewer system (32).

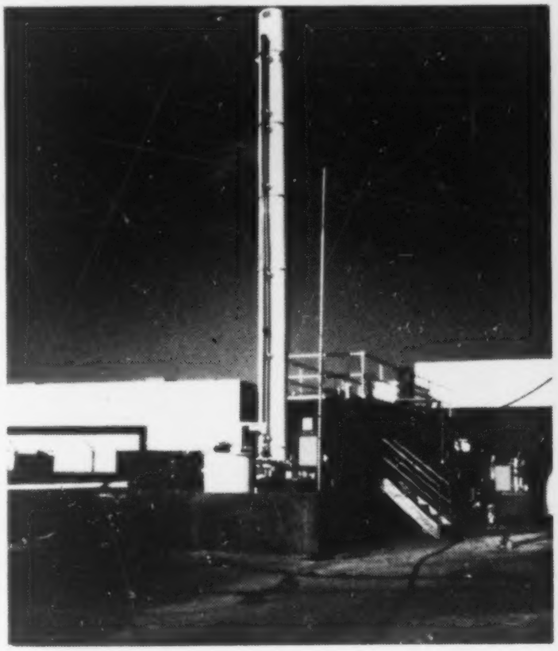

Photo credit: Ecova Corp.

An air stripper, combined with a bioreactor, detoxifies wastes at this Superfund site in San Jose, CA. The air stripper blows air at a cascade of groundwater to remove volatile hydrocarbons. The groundwater is then transferred to the bioreactor where soluble organics are degraded.

RESEARCH AND DEVELOPMENT FUNDING

Research and development funding for biotechnological approaches to waste management is modest compared with funding in other areas of biotechnology and comes from a variety of public and private sources. In addition to basic research, which has the potential for leading to innovations in all fields of biotechnology (supported by projects in genetics, molecular biology, microbial physiology, and ecology), the waste biotechnology field is supported by basic research concerned with toxic compounds, environmental sciences, physical-chemical sciences, and engineering.

Public Sector Investment

A substantial portion of basic research underlying biotechnology for waste management is supported by the public sector through the regular

Table 11-2.—Federal Expenditures for Biotechnology Applications to Waste Cleanup

Agency	Fiscal 1987 Dollars (in thousands)
Department of Defense	1,953
Department of Education	488
Department of Energy	920
Department of Interior	714
Environmental Protection Agency	3,497
National Aeronautics and Space Administration	350
National Institutes of Health	270
National Science Foundation	2,750
TOTAL	10,942

SOURCE: Office of Technology Assessment, 1988.

intramural and extramural programs of the Federal agencies. Federal agency funds specific to biotechnology for waste control are listed in table 11-2, for fiscal year 1987. EPA invested the most of any Federal agency, spending about $3.5 million on R&D related to biological systems for waste management. This is less than one-third of the total Federal investment, which OTA estimates at almost $11 million (table 11-2).

EPA Activities

The Environmental Protection Agency is the principal agency for conducting research and development for biotechnology and waste disposal. However, EPA is primarily a regulatory agency, and most of its R&D is geared to support regulatory activities. Thus, most biotechnology funds are directed toward developing methods for risk assessment. EPA also has some funds for developing products to clean up waste or products to mitigate risks of environmental damage. Funding levels for product development research are low, however, in accordance with EPA policy that the private sector should play a primary role in the development of products for commercial use (48).

Nonetheless, EPA laboratories are conducting a variety of small but significant research projects (see table 11-3). EPA also sponsors documentation and evaluation of new cleanup technologies through the Superfund Innovative Technology Evaluation (SITE) Program, and a coordinated Biosystems Initiative is planned for fiscal year 1989, pending budgetary approval. Many EPA projects involve innovative biological treatment technologies, but many do not involve genetic engineering, and so fall outside of EPA's definition of biotechnology (see ch. 3). Thus, funding figures reported in this chapter overlap with EPA funds reported in chapter 3 only for projects that involve genetic engineering of organisms for waste degradation.

SITE Program. The Superfund Innovative Testing and Evaluation (SITE) Program is authorized under the Superfund Amendments and Reauthorization Act of 1986. The SITE Program provides testing, sampling, and evaluation of innovative technology for hazardous waste cleanup. The proprietor of the technology pays for the demonstration itself, if private funding is available. If funding is not available, EPA can fund up to 50 percent, not to exceed $3 million, for any single demonstration. EPA accepted 12 technologies for testing and evaluation in the first round of selections for the SITE program in April 1987. One of these involves the microbial degradation of PCBs. In September of 1987, EPA selected 3 biologically based technologies out of a total of 10 for the second round of selections (39,45).

Funds have not yet been spent by EPA for the PCB-degradation project, but preliminary estimates indicate that testing and evaluation will cost about $200,000 (45). The owner of the technology says the SITE demonstration will cost him $50,000 and 1 year's time. He says that this demonstration will involve the bioremediation of 10 cubic yards of soil, although he has already demonstrated the technology on 14,000 cubic yards under State auspices. The SITE program, however, will provide the documentation and analysis to assure potential clients that the system works (26).

Biosystems Initiative. Recognizing the potential of biological systems for waste management, EPA proposed the Biosystems for Pollution Control Initiative, which, if approved, would begin in fiscal year 1989. The proposed initiative would provide about $4 million per year from 1989 to 1991 to develop, demonstrate, and evaluate biological technologies for waste cleanup (39). The Biosystems Initiative includes the following objectives:

- search out and characterize biodegradation processes in surface waters, sediments, soils,

Table 11-3.—EPA Projects in Biotechnology for Waste Management[a]

Project	Dollars (fiscal 1987)
Environmental Research Laboratory, Gulf Breeze, Florida	
TCE degradation	50,000
Complex waste sites	50,000
Anaerobic dehalogenation	unsupported
Suicide plasmids	120,000
Metabolic pathway recruitment	103,000
Extramural support (2,4,5-T degradation)	50,000
Hazardous Waste Engineering Laboratory Cincinnati, Ohio	
2,4,5-T degradation	50,000
White rot fungus	140,000
P. Chrysosporium	23,000
Yeast	88,000
PCB degradation	255,000
Plants	65,000
Biofilm reactor	66,000
Leachate slurries	112,000
Guidance document	50,000
Robert S. Kerr Environmental Research Laboratory Ada, Oklahoma	1,413,300
TCE-degradation	
Models for spilled hydrocarbons	
Models for soil cleanup	
Stanford demonstration project	
Water Engineering Research Laboratory Cincinnati, Ohio	
Genetics of methanogens	40,000
Microbial binding proteins	45,000
Prediction of biodegradation	210,000
Environmental Research Laboratory Athens, Georgia	
Anaerobic activity	14,000
Screening of indigenous organisms	70,000
Office of Exploratory Research (Extramural Grants)	482,571[b]
SITE Program	
Evaluation of PCB degradation	0[c]
TOTAL	3,496,871

[a] Excludes projects whose primary purpose is risk assessment.
[b] Figure represents one half of the total of five two-year grants, $965,143.
[c] Anticipated expenditures for FY88 are approximately $200,000.

SOURCE: Office of Technology Assessment, 1988.

and subsurface materials to identify processes that may be used in biological treatment systems;

- develop new biosystems for the treatment of pollutants, including genetically engineered and naturally selected micro-organisms, consortia, and bioproducts;
- determine, evaluate, and demonstrate the engineering factors necessary for the application of biological agents to detoxify or destroy pollutants;
- determine the environmental fate of and effects of and the risks involved in the use or release of biological agents or their products developed to detoxify or destroy pollutants;
- develop means to mitigate adverse consequences resulting from the accidental or deliberate release of biotechnology products developed for pollution control; and
- transfer information on the technology to promote its use (101).

EPA is marginally supporting various programs with long-term potential benefits. Program managers believe that many programs will have long-term payoff, but cannot be completed without additional funding. These programs include:

- genetically engineered anaerobic dehalogenators of chlorinated aromatics, which could be ready for commercialization and field application at Superfund sites within 3 to 4 years;
- immobilized ligninases isolated from white rot fungi, which could be used to oxidize chlorinated hydrocarbons within 3 to 5 years; and
- plant root fungi, which could be used to concentrate toxic metals from contaminated soils by 1992 (100).

EPA Research Laboratories. The Environmental Research Laboratory in Gulf Breeze, FL, is one of EPA's leading laboratories for research involving new biotechnologies. While their effort is focused on risk assessment for the release of novel organisms, several projects are focused on developing biotechnology to clean up hazardous waste. Gulf Breeze has projects to develop organisms to degrade trichloroethylene (TCE), to investigate the biology of complex waste sites; to investigate the anaerobic dehalogenation of hydrocarbons; to develop a "suicide plasmid" that would cause the organism to die once degradation of a target compound was complete; and to facilitate the transfer of metabolic pathways into new organisms. In addition, Gulf Breeze is supporting research at the University of Illinois on the microbial degradation of 2,4,5-T, an active ingredient in Agent Orange (66). The total cost of these projects was $373,000 in fiscal year 1987 (66).

The Hazardous Waste Engineering Research Laboratory (HWERL) in Cincinnati, OH, is the principal laboratory of the Office of Research and Development responsible for developing and evaluating technologies for hazardous waste control. HWERL has been supporting projects in biodegradation for several years (28). HWERL, along with Gulf Breeze, supports the 2,4,5-T work at the University of Illinois (66). HWERL also has a small biosystems program investigating the enzymes of the white rot fungus, which have been shown to reduce dioxins and other pollutants (39) and supports a range of extramural research projects in biodegradation. In addition, it is the lead laboratory in the Biosystems Initiative, described previously. The cost of these projects was about $850,000 in fiscal year 1987 (28).

The Robert S. Kerr Laboratory in Ada, OK, focuses on groundwater research and has identified a microbial process that may be capable of cleaning up TCE from aquifers and groundwater. The process is different from that used for TCE-degradation at the Gulf Breeze labs. This process relies on the ability of a group of naturally occurring microbes, called methanotrophs, to cooxidize trichloroethylene and a variety of other halogenated organic compounds when methane, propane, or natural gas is added. Researchers at Kerr Laboratory have demonstrated degradation using soil columns and are conducting field and laboratory tests in cooperation with Stanford University, the University of Oklahoma, and the Air Force (57). In the field tests, the bacteria degraded nearly 30 percent of the TCE in groundwater (1). Kerr Laboratory is also working to develop mathematical models for biosystems cleanups. The laboratory also has an active anaerobic biodegradation effort underway, as well as studies on subsurface microbiology.

EPA's Water Engineering Research Laboratory in Cincinnati supports several bioremediation projects. Projects include the study of the genetics of methanogens, with the long-term objective to improve the rate and reliability of anaerobic digestion; the study of microbial binding proteins, particularly the metallothionein enzyme, which is known to bind cadmium; and a study on the prediction of the biodegradation of toxic compounds based on structure-activity relationships. The laboratory has also worked to develop a protocol for evaluating bioaugmentation projects (106).

Microbial research at the Environmental Research Laboratory at Athens, GA, is concerned primarily with the fate of environmental pollutants. Research on the degradation of chlorinated compounds in anaerobic environments is an integral component of the in-house program. In addition, a 3-year cooperative program with New York University is looking at the stability of anaerobic consortia capable of degrading various organic pollutants (81).

EPA's Office of Exploratory Research supported five extramural research projects (all at universities) related to biological remediation systems for a 2-year total of $965,143 in 1986 and 1987. The extramural projects all involve in situ treatment, thus the emphasis on biological systems, and include bioenrichment with hydrogen peroxide, biodegradation of chlorinated aliphatic solvents, and other projects (17).

From 1982 to 1987, EPA also selected biodegradation for 4 Superfund sites, out of a total of 41 sites for which treatment technologies were used (102).

Cleanup of Federal Waste Sites

The Federal Government has been a substantial waste generator. The civilian Federal agencies have at least 1,882 potentially hazardous waste sites but have studied only half of them to determine whether cleanup is necessary. Of these, 1,326 sites belong to the Department of Energy (DOE); 1,061 of these were for the production of nuclear materials and weapons (5).

The Department of Defense (DoD) has also been a substantial waste generator, reporting 400 to 800 sites, which need remediation at a cost of $5 to $10 billion over the next 10 years. DoD supports a substantial research and development effort related to hazardous waste, in part as a response to the requirement to clean up its hazardous waste sites via their Installation Restoration Program (IRP), which is analogous to the Superfund. The DoD is collaborating with the EPA and DOE to develop demonstration projects at a total cost of $5 million (DoD's share is $1.953 million). A few of these relate to the use of biotechnology, according to the DoD program manager (27).

A significant portion of the DoD waste resulted from airplane engine cleaning solvents, airplane fuel spills, paint stripping, and nuclear waste. The Environics Division of the Research and Development Directorate of the Air Force is the service's principal laboratory for environmental research and development and maintains the lead in the DoD for biotechnology research and coordination with other Federal programs. The laboratory's work focuses on hazardous waste reduction; recovery and treatment of polluted soils; polluted groundwater treatment; and alternative energy sources. The laboratory funds both intramural projects (some funded jointly by EPA) and extramural programs, both in laboratories and at IRP sites. One project is funded jointly with DOE as a Small Business Innovation Research award.

The laboratory's research includes a wide-ranging program of 24 projects encompassing air and groundwater, containment chemistry, microbial degradation, and waste treatment. In-house research and program management staff includes 38 people, 9 holding doctorates, with an annual budget of $8 million. Six of the 24 projects use biological treatment of contaminants and several other projects provide background information to support biological methodology. Laboratories at Tyndall Air Force Base are investigating biological degradation of TCE, dioxin, and organometallics. They are attempting to isolate and modify micro-organisms capable of degrading contaminants, with particular interest in mixed culture systems and enhancement of conditions. Recombinant DNA modifications are used in the laboratory. Among other innovative technology projects is a contract to Cornell University to examine the use of *aphrons,* small (about 25 microns), stable bubbles, which serve both as a transport mechanism and as an oxygen source for biological agents to clean up aquifers.

Other Federal Research Activities

The Department of Energy (DOE) supports some research and development related to biotechnological approaches to waste management. Within the Deep Subsurface Microbiology Research Program, DOE supports projects involving 15 intramural and extramural researchers investigating microbial community structure and the factors that control microbial habitats and reactions at depths of 30 to thousands of meters, the depth of many of the nation's largest aquifers. These projects are aimed at in situ degradation of organic contaminants at DOE sites. The Ecological Research Division supports research on microbial fermentation of cellulose to methane and carbon dioxide, the mechanisms by which plants metabolize metals, and other plant processes. Through the DOE Small Business Innovation Research Program, five projects support bioenvironmental research and development. No studies on cost analyses of conventional versus biotechnological approaches could be identified at DOE. DOE supports some interagency research efforts with the Air Force and maintains contact with the Los Alamos and Idaho National Engineering Laboratories (31,95,96).

DOE's Idaho National Engineering Laboratories maintains a biotechnology unit with an interdisciplinary program, comprising molecular genetics, bioseparations, bioprocessing, biohydrometallurgy, and biochemical engineering focused on basic and applied microbiology relating to recovery of metal from ore and waste streams, removal of sulfur and metals from fossil fuels, solubilization and gasification of fossil fuels, degradation of toxic organic materials, and production and separation of proteins and carbohydrates. The laboratory is supported by the Department of Interior as well as by DOE (41,97).

The National Aeronautics and Space Administration (NASA), through its Controlled Ecological Life Support System (CELSS), supports work on waste conversion as part of its focus on maintaining life processes and recycling technology in closed systems. NASA also supports a limited amount of research on the metabolism of exotic organisms that live in unusual habitats, such as sea vents (6).

The National Science Foundation (NSF) supports about 10 projects for $2.5 million that are directly related to bioremediation of waste. One is a research center at the University of California at Los Angeles focused on engineering for hazardous substance control. The foundation also sponsors workshops on bioremediation (68).

The Department of Interior conducts several in-house projects on the bioleaching of manganese and supports research at Morehouse College on metallo-resistance. Interior, through the Bureau of Mines, also provides $500,000 to the Idaho National Engineering Laboratory for projects related to metals extraction and recovery and bio-assisted minerals processing.

The National Institute of Environmental Health Sciences has funded four research projects under authority granted in the Superfund Amendments and Reauthorization Act of 1986. Funds come from the Superfund Trust Fund. Research includes developing organisms tailored to degrade toxic waste, developing combinations of appropriate organisms, designing reactors, and defining operating conditions.

The Department of Education, through its Division of Higher Education Incentives, provided a grant of $488,000 in fiscal year 1987 to the University of Tennessee at Knoxville to establish a Center for Environmental Biotechnology, whose research focuses on environmental hazardous waste degradation (78).

Private Sector Investment

Investment by the private sector in waste management technologies is driven by regulation. Without regulation there would be little incentive for the major waste generators to minimize or clean up waste, and there would be a much smaller market for waste management services and technologies. Regulations also determine which waste cleanup technologies can be used.

New and stricter regulations are driving up the cost of traditional waste management services. Service providers who can find cheaper or safer methods of disposing wastes will have a clear advantage in today's markets. However, most waste management companies are small and cannot afford substantial R&D expenditures. Some of the large waste generators, on the other hand, can and do support R&D efforts. Biotechnology appears to be the subject of strong interest from venture capitalists interested in investing in waste management, although precise figures are not available.

An entire industry of small and not-so-small companies has sprung up to respond to the regulatory environment. These environmental companies range from engineering-oriented to biotechnically oriented, and a few are mixed. Twenty-one companies are listed in a recent directory as providing biological treatment services for hazardous waste material management. While substantially more companies are listed for chemical treatment and incineration (49 and 64 respectively) (40), the number of companies in biological treatment is significant and probably growing. A total of 65 companies, including waste generators, have been identified as involved in waste management biotechnology (see app. D).

The level of R&D investment in biotechnology for waste management by each company varies significantly. OTA has obtained figures for 1986 R&D expenditures from 10 of these 65 companies, which range from zero at one company to about $3 million at another. The 10 companies are all service providers, not waste generators.

In certain subspecialties, a substantial portion of even the most basic aspects of biotechnology research is supported by private funds. For example, the most advanced work on genes to degrade several of the chemicals listed on the National Priority List sites is being conducted in industrial laboratories.

Research and development costs at waste management companies cannot be separated cleanly from engineering costs and other costs of doing business. The industry's role is to provide scientific and engineering services, much of which could be considered R&D. Since each waste site is unique, each requires some original research before the best cleanup technology can be identified. In many cases, new engineering solutions must be developed that will enable degradation to occur while controlling the release or migration of contaminants. Some companies enter into research and development limited partnerships, in which the waste management company and the client (typically a waste generator) share ownership of whatever techniques are developed. R&D is thus based on what the client will buy.

RESEARCH AND DEVELOPMENT NEEDS

Research needs include microbial ecology, physiology, genetic expression and control, site engineering, site characterization, and feasibility studies. Numerous microbes with degradative capabilities have been identified and isolated. Other metabolic capabilities are still needed, however, and **the isolation of new strains of micro-organisms is an important area of research.** Many of those organisms already identified need refining and enhancement to be useful for field application; these activities require research investment. Site engineering and feasibility studies require that the metabolites produced be understood and that the migration of compounds in the environment be predictable. Knowledge of surfactants and emulsifiers, often needed for the microbes to react with the target compound, is also required.

Basic Research Needs

The lack of knowledge of microbial physiology and ecology is a major scientific stumbling block from the standpoints of efficacy, efficiency, economics, and environmental safety. While molecular biology has had several decades of stable funding, microbial ecology has lagged behind, and suddenly the need for information about microbial ecosystems is acute (24,71).

Identifying and selecting organisms to alter waste continues to be an important area of endeavor. While many of micro-organisms have been located with propitious characteristics, other organisms with even more advantages can probably be found (22,63).

Interest in anaerobic degradation has increased in recent years. Anaerobes may circumvent the need for oxygen in some applications. Anaerobes are also likely to produce novel reactions, such as the dechlorination reaction described previously, that could provide key steps in degrading target chemicals. Knowledge of the biology and genetic manipulation of anaerobes, however, lags behind that for aerobes (61).

For wastes that resist degradation by known organisms, engineering new organisms might be appropriate. To genetically engineer microbes for specific waste problems, the genes of interest and their control elements need to be identified. As can be seen in table 11-1, many degradative organisms have been identified, but the pathways, enzymes, and genes involved in degradation are often unknown. Genes for other processes, such as production of energy, surfactants, and emulsifiers also need to be identified if these traits are to be genetically engineered.

Applied Research Needs

Keeping the degrading organism alive and active and providing access to target compounds are the two most basic needs in applying biotechnology to pollution problems. Strategies include providing oxygen and nutrients and exploiting microbial symbiosis. The potential advantages of creating engineered organisms with all the required capabilities versus creating mixed communities of specialist organisms are not known. However, researchers are reluctant to deal with engineered organisms when alternatives are available.

Biodegradation requires making the target compound available to the organisms. Pollutants frequently occur attached to solids, mixed as hydrophobic and hydrophilic waste, or as low molecular weight semi-volatiles in groundwater, often making them inaccessible to microbes. Molecular and engineering strategies to make pollutants available to organisms are poorly developed. Surfactants and emulsifiers produced by naturally occurring organisms should be investigated.

Information on the characteristics and measurement of pollutants is only partly developed (76, 104), especially with regard to chemically similar compounds, called congeners. Extreme and varied concentrations of compounds, known as hot spots, complicate assessment (76). Measuring groundwater contamination in situ, for example, is problematic (70).

Careful and thorough demonstration and evaluation studies of bioremediation techniques are also required. Current practice frequently relies on a single line of evidence for the disappearance of one pollutant and relies on samples from a few spots in an uneven mixture. Lack of information in this area leads to a lack of credibility regarding the effectiveness of cleanup efforts. In at least one case of putative degradation, for example, an organism was thought to have degradative capabilities because a target compound disappeared from the medium in which the organism was grown. It turned out the compound had not been degraded but absorbed by the organism, a useful property but not one that actually degrades or detoxifies the pollutant. **Comparative data regarding the relative efficacy, economics, and environmental safety of biotechnical versus conventional methods are seriously lacking.**

BARRIERS TO DEVELOPMENT OF THE TECHNOLOGY

Although the potential advantages of innovations in biotechnological approaches for waste management are recognized, it is generally accepted that the development of biotechnology products for hazardous waste management is lagging behind product development in other sectors of the biotechnology industry, such as pharmaceutical and agricultural applications (104). The barriers to innovative applications lie in several areas, including funding, regulations, personnel, and economics.

Funding and Programmatic Implementation

Technical and scientific barriers to biotechnological waste management are discussed in the previous section on "Research and Development Needs." Knowledge gaps result from uneven funding for basic research in certain fields, such as microbial ecology, and from the fragmented and uncoordinated nature of funding for R&D of biotechnological approaches to hazardous waste management. Funding is fragmented for these reasons:

- Neither the public nor the private sector takes responsibility for funding basic or generic applied research in important areas. Microbial physiology and ecology have not been well supported by any agency or other resource.
- Technical and scientific advancement of the waste field is strongly linked to regulations and to the funding programs of a single lead

agency. The amount of funding available supports only a few researchers and projects, and the available funding lacks a coherent program to develop the necessary technical and scientific base in identified critical areas. In addition, EPA's enforcement efforts and regulatory authority were in a state of flux in the early 1980s (23), which reduced the private sector's incentives for research (26).

Problems With Private Investment

Waste management companies face a range of disincentives to investing in bioengineered approaches to waste management, from regulatory uncertainty to R&D expense. Waste management companies focus development efforts on technologies that have been developed by others and that can be purchased ready for commercialization, thus avoiding the R&D risk.

Waste companies also favor technologies in which the treatment times and effluent concentrations can be predicted with reliability, even when the costs are much higher, in order to reduce potential liability. Bioengineered approaches are almost never as predictable, at least with current knowledge, as nonbiological alternatives (8,9).

Since much of the waste management and cleanup market involves the remediation of complex waste sites, companies may prefer to invest in techniques better suited to handle complex mixtures of waste. Complex waste sites are currently beyond the capabilities of biotechnological waste management techniques.

Problems With Public Investment

Both researchers and industrial managers say they believe that EPA does not provide clear management with regard to developing the field scientificially and does not manage its programs from a broad enough perspective to give appropriate weight to biotechnological approaches. Questions about the best implementation of the program have been raised many times (59,63,92,104), but have not been resolved. These include:

- developing clear standards,
- developing assessment technologies to support implementing these standards, and
- conducting clear, comparative studies of biotechnology and conventional approaches to hazardous waste treatment to answer the efficacy, economic, and safety questions that face the field.

Regulatory programs have strongly directed the patterns of the research conducted. As EPA's experience has been largely with land disposal and incineration, some believe that staff at the agency are poorly equipped to deal with biotechnology. For example, access to federally designated sites for demonstration projects appears weighted in favor of nonbiological approaches (26,79,86,102). While many innovative nonbiological methods are also worthy of testing and evaluation, biological methods clearly will not be fully developed without additional testing and evaluation.

Funding by the EPA is insufficient and comparatively unstable. The Agency is funding high-quality in-house research, but at a level too low to develop biotechnology's potential for hazardous waste detoxification. Unstable funding of extramural projects, in particular, prevents initiating long-term projects. For example, a leading researcher with demonstrated ability to produce organisms tailored to degrade toxic substances believes that he could develop a micro-organism that would degrade dioxin (21,64). Development would require stable funding of $125,000 per year for 5 to 7 years. The project would require a high-quality and experienced postdoctoral fellow, but the researcher cannot in good faith recruit such a person because even funded projects are subject to cancellation by EPA. This project is not suitable for students or postdoctoral fellows for a short period, both because it requires dedicated expertise and because researchers at those stages in their careers must have projects that produce results in time for them to write a dissertation or secure a job. In addition, the toxicity of the compound being examined suggests the need for designated research facilities with researchers specially trained in necessary safety measures. In short, this project and others like it will not be accomplished without a stable, long-term commitment (21).

Until the critical research areas are addressed and performance standards are clearly established, cleanup claims offered by

individual companies will lack credibility. Only studies conducted without conflict of interest will resolve efficacy, economic, and environmental safety questions.

Regulation

Regulation dictates what must be cleaned up, how clean it must be, and which cleanup methods may be used. Thus, regulation determines what is developed for the waste field. Currently, regulation favors the use of contained cleanup methods and the use of naturally occurring, indigenous organisms. Although no recombinant organism is ready for field trial, such an organism eventually will be ready. However, **fears of regulatory barriers are discouraging researchers from investigating genetic engineering as a means of developing novel, potentially beneficial, organisms.**

Individual companies have reported great difficulty in getting approval or support from EPA for biological approaches or even access to sites for demonstration projects. Company research directors and presidents have complained that EPA is biased toward nonbiological approaches, and that it is extremely difficult to get regulators to consider biological techniques (26,86).

In addition, HSWA defines land disposal to include land treatment. Thus, with the onset of the Land Disposal Restrictions, RCRA-listed hazardous waste cannot be placed in or on the land for eventual biodegradation, even as a landfarming experiment, unless a petitioner can prove the waste will not migrate for as long as it remains hazardous (109). Furthermore, obtaining the RCRA permit takes approximately 4 years. A research, development, and demonstration permit can be obtained in about 8 months (109).

Regulatory resistance to bioremediation stems from a variety of factors. One prominent problem is that bioremediation techniques have been oversold in the past, so the field lacks credibility. Many applications are new and do not have any history of effectiveness. A second problem involves time limitations: certain biological applications take longer than incineration or excavation. Although they may be cheaper or more thorough, bioremediation techniques may be passed over due to the desire to address the problem as quickly as possible. In addition, performance standards have been established only for land disposal and incineration. Finally, engineers, who are often the regulators, may not be familiar with the biology involved in these cleanup systems. EPA frequently does not have adequate data for evaluating biotechnology. No regulations require companies to compile and submit data on alternative technologies. Also, companies often do not want anyone to know they have a hazardous waste problem and thus do not make their information public.

Personnel

A serious impediment to greater use of bioremediation techniques is the lack of technical understanding by regulatory enforcement personnel (86) and by many EPA contractors involved in waste management. In some cases, officials have relied on bioremediation data from the 1970s (86) despite the numerous advances made in recent years. Small businesses with waste problems have testified to the reluctance on the part of regulators to accept the possibility that biodegradation works (86).

Despite testimony from EPA scientists that biodegradation may be applicable to many Superfund sites (86), EPA apparently does not see the need to increase its expertise in biology in the Superfund program. Personnel with expertise in the biological sciences constituted 25 of 1,643 full-time equivalents in the Superfund program in fiscal year 1986, or 2 percent of the total (105). An EPA work force planning study concluded that Superfund's current and strong orientation toward engineering and physical/environmental sciences was appropriate for future field operations. On the basis of anticipated trends and changes in the program, the following occupation areas were reported to be underrepresented among Superfund staff: hydrology, geology, and procurement and contracts (105). Such a conclusion, if heeded, does not indicate that EPA will increase its expertise in the biological sciences and bioremediation techniques. An EPA administrator, however, has suggested that if the agency develops the necessary knowledge base in biotechnology, it is possible that EPA would begin to recommend microbial degradation for RCRA corrective actions (109).

Since the application of biotechnology to hazardous waste management is relatively new, the infrastructure for training is underdeveloped. The field requires bioengineers with interdisciplinary training in chemical and civil engineering and biology as well as hydrogeologists with expertise in biology (16). Additional personnel with expertise in microbial ecology are also required (see ch. 8) (87). Underfunding of microbial ecology in the past has led to a shortage of expertise.

Economic Uncertainty

Whether conventional methods or biotechnologies offer more economic potential to clean up waste is under debate. Small, young biotechnology firms, in particular, cannot afford the high risk, uncertain-payoff R&D efforts required to develop new technologies. Uncertainty about regulations and liability also discourages some firms from pursuing innovative technologies. EPA is, however, addressing this problem with a small conference to bring entrepreneurs, venture capitalists, and EPA regulators together to clarify potential opportunities (43).

Theoreticians argue that, once the technology is developed, biological degradation is always cheaper than chemical treatment or burning because the organism supplies a catalyst that works at ambient temperatures and, if designed well, generates its own energy, without additives. Others argue that the high up-front cost of biotechnology research and development brings the economic projections for the two approaches closer together.

The need to develop specific solutions for each in situ cleanup adds to economic uncertainty. Each site has unique characteristics, ranging from the type of contaminant to soil porosity to local politics. A treatment system developed for one site may or may not be applicable to other sites.

ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

ISSUE 1: Should research and development in biotechnology for waste management be stimulated?

Option 1.1: Take no action.

Biotechnology for waste management has suffered in recent years from various funding and institutional barriers. Its development is in a relative state of infancy compared with that of biotechnology in pharmaceuticals and agriculture. However, public and private interest in biotechnology for waste management is increasing without specific congressional action. Nonetheless, without some initiatives, key research barriers are likely to go unaddressed for several years or longer and adequate efficacy and efficiency demonstrations will not be carried out. Without specific action, the relevant agencies, in particular EPA, are not likely to develop in-house scientific and managerial expertise for the assessment and regulation of bioremediation techniques.

Option 1.2: Increase funding for research in biodegradation activities.

Increased funding for research and development in biotechnology for waste management could bring attention to key research areas that are currently bottlenecks in the application of the technology, such as microbial physiology and ecology, genetic engineering of anaerobes, and the development of specific degradative pathways for key persistent compounds, such as dioxin. Additional funds could also facilitate demonstration and evaluation projects, which require support from government or other disinterested parties if results are to be unbiased and credible. For example, with funds to increase its expertise in biology, EPA would be better able to evaluate potential research and development projects, demonstration projects, and cleanup projects that use innovative biological methods. Without such funding, EPA will continue to fund only certain high priority projects, and at relatively low levels.

Option 1.3: Provide funds for training programs in disciplines related to waste management biotechnology, including microbial ecology, biohydrogeology, and environmental engineering with emphasis in biotechnology.

The successful development of waste management biotechnology requires a wide range of expertise in the waste management industry, in State and Federal regulatory agencies, and in research universities. The predominance of personnel with experience in land disposal and incineration in the waste management field has left biological and other innovative technologies with an uphill battle for acceptance. A training strategy should be two-pronged, including both training current engineers in biology and the training of new environmental engineers in bioremediation.

Option 1.4: Clarify and enforce existing regulations regarding hazardous waste cleanup and disposal.

The claim has been made that existing regulations are not being fully or uniformly enforced. Standards for cleanup are also not always clear and can change. Enforcing existing regulations will ensure that more cleanup technologies are used and will create incentives for developing more cost-effective technologies.

Option 1.5: Establish more stringent standards to require permanently remediated and ecologically sound sites.

Regulations drive the field of waste management. The current Superfund program established cleanup standards that emphasize permanent remedies. However, RCRA standards are generally less stringent. Also, performance standards for bioremediation are less well developed than those for incineration or land disposal. Such performance standards need to be clarified. Regulations requiring permanent disposal of wastes could spur the development of technologies that will detoxify or destroy wastes and leave products that can be returned to use in the environment.

ISSUE 2: Is the management and regulation of biological cleanup technologies adequate and appropriate?

Option 2.1: Take no action.

In the current system, both basic and applied R&D is supported by a variety of public and private organizations, including several Federal agencies and private companies. However, neither the public nor private sector takes responsibility for many basic and strategically important research and development areas. As a result, there is no coherent program for overall management of R&D and no strategy for developing the field. Key research barriers are not being addressed, and demonstration and evaluation projects are lacking. A limited number of innovative technologies are being attempted through programs such as the Superfund Innovative Technology Evaluation (SITE) program. Without some management initiative, the field cannot be expected to develop in a timely manner. EPA's Biosystems Initiative is a first step in this direction, but EPA's principal focus is regulation, not research and development. The present system may, however, protect the public from excessive or irresponsible applications of bioengineered cleanup approaches that could exacerbate, without solving, the problem.

Option 2.2: Establish an interagency coordinating body to create strategies for developing biological cleanup technologies.

Currently, EPA, the National Science Foundation, the National Institutes of Health, the Department of Interior, the Department of Energy, and the Department of Defense have significant programs related to bioengineered waste cleanup technologies. An interagency coordinating group could identify major gaps in the research and work to prevent unnecessary duplication of efforts by Federal agencies. This option would not necessarily cost the government more money, nor would it ensure more money would go for research.

Option 2.3: Clarify regulations on the environmental application of genetically engineered organisms.

The private sector favors activities involving nonengineered organisms due to the uncertainty surrounding regulations for engineered organisms. While nonengineered organisms are frequently effective and appropriate, opportunities may be missed if genetic engineering is not explored. Congress could encourage the use of genetically engineered organisms for waste cleanup by resolving the issues of deliberate release of novel organisms. Adopting this option could lead to the creation of organisms with important new degradative capabilities.

SUMMARY AND CONCLUSIONS

Biotechnology offers real possibilities for providing permanent solutions to hazardous and nonhazardous environmental wastes. Most of its potential, however, remains unrealized due to technical, institutional, economic, and perceptual barriers. Progress is being made in each of these areas.

Interest in waste management biotechnology is growing in the public and private sector, but the field continues to suffer from a lack of personnel in regulatory agencies and in the waste management industry who understand biology. The field suffers from a credibility problem brought about partly by earlier claims that were not supported by scientific fact and partly by the inertia in the waste management community that favors traditional methods of land disposal and incineration. In addition, much fundamental research is needed if biological techniques are to achieve high rates of destruction on a broad range of toxic wastes. There is a strong need for demonstrating and evaluating innovative bioremediation techniques. EPA has begun to move in this direction with the SITE program and the proposed Biosystems Initiative.

Many chemical waste sites are amenable to biodegradation, and practical applications are underway. Many other potential applications require substantial amounts of research and development before field trials can be attempted. Much work with naturally occurring or laboratory-selected strains can proceed, avoiding the perceptual and regulatory problems of using genetically engineered micro-organisms.

However, current applications of biological remediation techniques are generally suited to a limited range of pollutants in accessible conditions. Expanding the range of wastes amenable to bioremediation and degrading those wastes in the environments in which they occur to the very low concentrations needed may, ultimately, require genetic engineering. Engineering such microbes will require a substantial investment in R&D, and may face significant problems of public perception. Regardless of how the organisms are derived, thorough knowledge of waste ecology, of degradative intermediates and end products, and of the migration of both the organisms and the chemicals is needed.

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Appendixes

Appendix A

Dedicated Biotechnology Companies (DBCs) by State

Alabama

Southern Biotech Associates
P.O. Box 26221
Birmingham, AL 35226

Arizona

Bio Huma Netics
201 Roosevelt Ave.
Chandler, AZ 85226

Vega Biotechnologies, Inc.
P.O. Box 11648
Tucson, AZ 85734

Arkansas

Pel-Freeze Biologicals, Inc.
P.O. Box 68
Rogers, AR 72757

California

Advanced Genetic Sciences
6701 San Pablo Ave.
Oakland, CA 94608

Advanced Genetics Research Institute
2220 Livingston St.
Oakland, CA 94606

Agouron Institute
505 Coast Blvd., South
La Jolla, CA 92037

American Biogenetics Corp.
19732 Macarthur Blvd.
Irvine, CA 92715

American Bionetics, Inc.
4560 Horton St.
Emeryville, CA 94608

American Qualex Int'l., Inc.
14620 E. Firestone Blvd.
La Mirada, CA 90638

Amgen
1900 Oak Terrace Lane
Thousand Oaks, CA 91320

Antibodies, Inc.
P.O. Box 1560
Davis, CA 95617

Applied Biosystems
850 Lincoln Center Dr.
Foster City, CA 94404

Automedix Sciences, Inc.
9401 S. Vermont Ave., Suite B100
Torrance, CA 90502

Behring Diagnostics
10933 N. Torrey Pines Rd.
La Jolla, CA 92037

Berkeley Antibody
4131 Lakeside Dr., Suite B
Richmond, CA 94806

Biogenex Laboratories
6549 Sierra Lane
Dublin, CA 94568

Bio-Rad Laboratories, Inc.
1414 Harbour Way South
Richmond, CA 94804

Bio Research, Inc.
11189 Sorrento Valley Rd.
San Diego, CA 92121

Bio-Response, Inc.
1978 W. Winton Ave.
Hayward, CA 94545

Biogrowth
3065 Atlas Rd., Suite 117
Richmond, CA 94806

Bioprobe International, Inc.
2842 Walnut Ave., Suite C
Tustin, CA 92680

Biosearch, Inc.
2980 Kerner Blvd.
San Rafael, CA 94901

BioSym Technologies
10065 Barnes Canyon Rd., Suite A
San Diego, CA 92121

Biotherapy Systems, Inc.
291 N. Bernardo Ave.
Mountain View, CA 94043

Biotrack
430 Oakmead Parkway
Sunnyvale, CA 94806

Breit Laboratories
2510 Boatman Ave.
W. Sacramento, CA 95691

Brunswick/Technetics
4116 Sorrento Valley Rd.
San Diego, CA 92121

BTX
3742 Jewell St.
San Diego, CA 92109

Calgene, Inc.
1920 5th St.
Davis, CA 95616

California Biotechnology, Inc.
2450 Bayshore Frontage Rd.
Mountain View, CA 94043

California Integrated Diagnostics
1440 Fourth St.
Berkeley, CA 94710

California Biotherapeutics
10901 N. Torrey Pines Rd.
La Jolla, CA 92037

Calzyme Laboratories, Inc.
3443 Miguelito Ct.
San Luis, CA 93401

Cetus Corp.
1400 Fifty Third St.
Emeryville, CA 94608

Chemicon International, Inc.
100 Lomita St.
El Segundo, CA 90245

Chiron Corp.
4560 Horton St.
Emeryville, CA 94608

Clontech Laboratories, Inc.
4055 Fabian Way
Palo Alto, CA 94303

Codon
430 Valley Dr.
Brisbane, CA 94005

Collagen Corp.
2500 Faber Pl.
Palo Alto, CA 94303

Cooper Development Co.
3145 Porter Dr.
Palo Alto, CA 94304

Cryschem, Inc.
5005 LaMart Dr., Suite 204
Riverside, CA 92507

Cygnus Research Corp.
701 Galveston Dr.
Redwood, CA 94063

Cytotech, Inc.
11045 Roselle St.
San Diego, CA 92121

Dako Corp.
22 North Milpas St.
Santa Barbara, CA 93103

Diagnostic Products Corp.
5700 W. 96 St.
Los Angeles, CA 90045

Dnax
901 California Ave.
Palo Alto, CA 94304

E-Y Laboratories, Inc.
107 N. Amphlett Blvd.
San Mateo, CA 94401

Engenics, Inc.
3760 Haven Ave.
Menlo Park, CA 94025

Enzon
518 Logue Ave.
Mountain View, CA 94043

Fermentec Corp.
101 First St., Suite 490
Los Altos, CA 94022

Gen-Probe, Inc.
9880 Campus Point Dr.
San Diego, CA 92121

Genenchem
460 Point San Bruno Blvd.
S. San Francisco, CA 94080

Genencor, Inc.
180 Kimball Way
S. San Francisco, CA 94080

Genentech
460 Point San Bruno Blvd.
S. San Francisco, CA 94080

Gensia Pharmaceuticals, Inc.
11180 Roselle St., Suite A
San Diego, CA 92121-1207

Hana Biologics, Inc.
8050 Marina Village Parkway
Alameda, CA 94501-1034

Hybritech, Inc.
11095 Torreyana Rd.
San Diego, CA 92121

Idec, Inc.
11211 Sorrento Valley Rd., Suite H
San Diego, CA 92121

Idetek, Inc.
1057 Sneath Lane
San Bruno, CA 94066

The Immune Response Corp.
8950 Villa La Jolla Dr., Suite 1200
La Jolla, CA 92037

Immunetech Pharmaceuticals
11045 Roselle St.
San Diego, CA 92121

Infergene Co.
433 Industrial Way
Benicia, CA 94510

Ingene, Inc.
1545 17th St.
Santa Monica, CA 90404

Intek Diagnostics, Inc.
1450 Rollins Rd.
Burlingame, CA 94010

Intelli-Genetics
700 East El Camino
Mountain View, CA 94040

International Enzymes, Inc.
1667 S. Mission Rd.
Fallbrook, CA 92028

International Plant Research Institute
830 Bransten Rd.
San Carlos, CA 94070

Kirin-Amgen
Amgen, 1900 Oak Terrace Lane
Thousand Oaks, CA 91320

Lee Biomolecular Research Labs
11211 Sorrento Valley Rd.
San Diego, CA 92121

Liposome Technology
1050 Hamilton Ct.
Menlo Park, CA 94025

Lucky Biotech Corp.
4560 Horton St.
Emeryville, CA 94608

Microbio Resources
6150 Lusk Blvd., Suite B105
San Diego, CA 92121

Microgenics
2341 Stanwell Dr.
Concord, CA 94520

Molecular Biosystems, Inc.
11180 Roselle St., Suite A
San Diego, CA 92121

Molecular Devices
3180 Porter Dr.
Palo Alto, CA 94034

Monoclonal Antibodies, Inc.
2319 Charleston Rd.
Mountain View, CA 94043

Moor Associates
2190 Crestmoor Dr.
San Bruno, CA 94066

Multiple Peptide Systems, Inc.
558 Ford Ave., P.O. Box 5000
Solana Beach, CA 92705

Mycogen
5451 Oberlin Dr.
San Diego, CA 92121

NeuroScience Inc.
1520 McCandless Dr.
Milpitas, CA 95035

Neushul Mariculture
475 Kellogg Way
Goleta, CA 93117

NMS Pharmaceuticals
1533 Monrovia Ave.
Newport Beach, CA 92663

Ocean Genetics
140 Dubois St.
Santa Cruz, CA 95060

Omni Biochem, Inc.
2215 Cleveland Ave.
National City, CA 92050

Organon Diagnostics
316 Prospect St.
La Jolla, CA 92037

Pacific Biotech Inc.
8535 Commerce Ave.
San Diego, CA 92121

Penninsula Laboratories, Inc.
611 Taylor Way
Belmont, CA 94002

Pharmatec, Inc.
9401 S. Vermont Ave., Suite B100
Torrance, CA 90502

Phytogen
101 Waverly Ave.
Pasadena, CA 91105

Plant Genetics, Inc.
1930 Fifth St.
Davis, CA 95616

Protein Design Labs
3181 Porter Dr.
Palo Alto, CA 94304

Quidel
11077 N. Torrey Pines Rd.
La Jolla, CA 92037

Research and Diagnostic
Antibodies
P.O. Box 7653
Berkeley, CA 94707

Salutar, Inc.
428 Oakmead Parkway
Sunnyvale, CA 94806

Scripps Laboratories
9950 Scripps Lake Dr.
San Diego, CA 92131

Sepragen
2126 Edison Ave.
San Leandro, CA 94577

Sibia
P.O. Box 85200
San Diego, CA 92138

Stratagene Cloning Systems
3770 Tansy St.
San Diego, CA 92121

Sungene Technologies Corp.
3330 Hillview Ave.
Palo Alto, CA 94304

Synbiotics Corp.
11011 Via Frontera
San Diego, CA 92129

Synthetic Genetics
10457 Roselle St., Suite E
San Diego, CA 92121

Syntro Corp.
10655 Sorrento Valley Rd.
San Diego, CA 92121

Syva Co.
900 Arastradero Rd.
Palo Alto, CA 94304

Techniclone International, Inc.
3301 South Harbor Blvd.
Suite 101
Santa Ana, CA 92704

Telios Pharmaceuticals
2909 Science Park Rd.
San Diego, CA 92121

Three-M (3M) Diagnostic Systems
1500 Salado Dr.
Mountain View, CA 94043

Triton Biosciences, Inc.
1501 Harbor Bay Parkway
Alameda, CA 94501

Vector Laboratories, Inc.
30 Ingold Rd.
Burlingame, CA 94010

Viagene, Inc.
11180 Roselle St., Suite A
San Diego, CA 92121

Westbridge Research Group
9920 Scripps Lake Dr.
San Diego, CA 92131

Xoma Corp.
2910 Seventh St.
Berkeley, CA 94710

Xytronyx, Inc.
6555 Nancy Ridge Dr.
San Diego, CA 92121

Zoecon Corp.
975 California Ave.
Palo Alto, CA 94304

Zymed Laboratories, Inc.
52 S. Linden Ave., Suite 4
S. San Francisco, CA 94080

Colorado

Advanced Mineral Technologies
5920 McIntyre
Golden, CO 80403

Agrigenetics
3375 Mitchell Lane
Boulder, CO 80301

Amgen Development Corp.
2045 32nd St.
Boulder, CO 80301

Biostar Medical Products, Inc.
5766 Central Ave.
Boulder, CO 80301

Coors Biotech Products Co.
(subsidiary of Coors Brewing Co.)
Mail #CC150
Golden, C0 80401

Genetic Engineering, Inc.
136 Avenue and North
Washington St.
PO-33554
Denver, CO 80233

Synergen, Inc.
1885 33rd St.
Boulder, CO 80301

Synthetech
5547 Central Ave.
Boulder, CO 80301

Techometrics, Inc.
1960 Sherrelwood Circle
Denver, CO 80221

Connecticut

Agotek
1465 Post Rd. East, PO-5117
Westport, CT 06881

American Diagnostica, Inc.
111 North St.
Greenwich, CT 06830

Biopolymers, Inc.
309 Farmington Ave.
Farmington, CT 06032

John Brown E&C Inc.
P.O. Box 1432, 17 Amelia Pl.
Stamford, CT 06904

Chimerix
P.O. Box 976, 55 Nye Rd.
Glastonbury, CT 06033

Deltown Chemurgic Corp.
191 Mason St.
Greenwich, CT 06830

Intl. Biotechnologies, Inc.
275 Winchester Ave.
P.O. Box 9598
New Haven, CT 06511

Microgene Systems
400 Frontage Rd.
West Haven, CT 06516

Molecular Diagnostics, Inc.
400 Morgan Lane
West Haven, CT 06516

Novo Labs, Inc.
59 Danbury Rd.
Wilton, CT 06897

Technology Management Group
25 Science Park
New Haven, CT 06511

University Genetics Co.
1465 Post Road East
Westport, CT 06881

Xenogen
1734 Storrs Rd.
Mansfield, CT 06268

Delaware

Triad Technologies, Inc.
308 W. Basin Rd.
New Castle, DE 19720

District of Columbia

Alpha I Biomedicals
777 14th St., N.W., Suite 747
Washington, DC 20005

Florida

Applied Genetics Labs., Inc.
3150 S. Babcock St.
Melbourne, FL 32901

Diamedix, Inc.
2140 N. Miami Ave.
Miami, FL 33127

Immunomed
5910-G Breckenridge Parkway
Tampa, FL 33610

Innovet
3401 N. Federal Highway
Boca Raton, FL 33431

Life Sciences
2900 72nd St., North
St. Petersburg, FL 33710

Molecular Genetic Resources
6201 Johns Rd., Suite 8
Tampa, FL 33634

Petroferm USA
5400 First Coast Highway,
Suite 200
Ferandina Beach, FL 32034

Viragen
2201 W. 36th St.
Hialeah, FL 33016

Georgia

Biosystems, Inc.
762 U.S. Highway 78
Loganville, GA 30249

Murex Corp.
P.O. Box 2003
Norcross, GA 30071

Hawaii

Hawaii Biotechnology Group, Inc.
99-193 Aiea Heights Dr.
Aiea, HI 96701

Illinois

Ball Biotech Co.
250 Town Rd.
W. Chicago, IL 60185

Dekalb-Pfizer Genetics
3100 Sycamore Rd.
De Kalb, IL 60115

Petrogen, Inc.
2452 East Oakton
Arlington Heights, IL 60005

United Agriseeds, Inc.
P.O. Box 4011
Champaign, IL 61820

Indiana

Agdia, Inc.
1901 N. Cedar St.
Mishawaka, IN 46545

BioProducts for Science, Inc.
P.O. Box 29176
Indianapolis, IN 46229

Consolidated Biotechnology, Inc.
1413 W. Indiana Ave.
Elkhart, IN 46515

Iowa

Ambico, Inc.
P.O. Box 522, Route 2
Dallas Center, IA 50063

Kansas

Clinical Biotechnologies, Inc.
11844 W. 85th St.
Lenexa, KS 66214

Hazelton Research Products
P.O. Box 14848
Lenexa, KS 66215

Monoclonal Production Int'l.
Twentieth and Sydney Sts.
Fort Scott, KS 66701

Syngene Products
15 and Oak, P.O. Box 338
Elwood, KS 66024

Louisiana

Helix Corp.
635 Louisiana Ave.
Baton Rouge, LA 70802

Imreg, Inc.
144 Elk Pl., Suite 1400
New Orleans, LA 70112

Microbe Masters
11814 Corsey Blvd., Suite 285
Baton Rouge, LA 70802

Maine

Agritech Systems, Inc.
104 Fore St.
Portland, ME 04101

Atlantic Antibodies
10 Nonesuch Rd.
Scarborough, ME 04704

Binax, Inc.
95 Darling Ave.
S. Portland, ME 04106

Immucell Corp.
966 Riverside St.
Portland, ME 04103

Ventrex Laboratories
217 Read St.
Portland, ME 01403

Maryland

Advanced Biotechnology, Inc.
12150 Tech Rd.
Silver Spring, MD 20904

American Biotechnology Co.
7658 Standish Pl., Suite 107
Rockville, MD 20855

Andrulis Research Corp.
7315 Wisconsin Ave., Suite 650N
Bethesda, MD 20814

BBL Microbiology Systems
(Division of Becton-Dickinson & Co.)
Box 243, 250 Schilling Circle
Cockeysville, MD 21030

Bionetics Research, Inc.
1330 Piccard Dr.
Rockville, MD 20850

Biospherics
4928 Wyaconda Rd.
Rockville, MD 20852

Biotech Research Labs, Inc.
1600 E. Gude Dr.
Rockville, MD 20850

Biotronic Systems Corp.
15225 Shady Grove Rd., Suite 306
Rockville, MD 20850

Braton Biotech, Inc.
1 Taft Ct.
Rockville, MD 20850

Cellmark Diagnostics
20271 Goldenrod Lane
Germantown, MD 20874

ChemGen Corp.
2501 Research Blvd.
Rockville, MD 20850

Crop Genetics International
7170 Standard Dr.
Hanover, MD 21706

Design Engineering and Manufacturing Co., Inc.
4906 46th Ave.
Hyattsville, MD 20781

Diagnon Corp.
11 Taft Ct.
Rockville, MD 20850

Digene
Bldg. 334
University of Maryland
College Park, MD 20742

Electro-Nucleonics, Inc.
Cell Science Institute
12050 Tech Rd.
Silver Spring, MD 20904

Genex, Inc.
16020 Industrial Dr.
Gaithersburg, MD 20877

Gentronix, Inc.
12150 Tech Rd.
Silver Spring, MD 20904

Igen
1530 E. Jefferson St.
Rockville, MD 20852

Igene Biotechnology, Inc.
9110 Red Branch Rd.
Columbia, MD 21405

ImmuQuest Laboratories, Inc.
2 Taft Ct., Suite 101
Rockville, MD 20850

In Vitro International, Inc.
611P Hammonds Ferry Rd.
Linthicum, MD 21090

Inter-American Research Association
1160 Taft St.
Rockville, MD 20850

Keystone Diagnostics, Inc.
9062 Route 108
Columbia, MD 21405

Life Technologies, Inc.
8717 Grovemont Circle
Gaithersburg, MD 20877

Loftstrand Laboratories
8042 Cessna Ave.
Gaithersburg, MD 20879

Microbiological Associates
5221 River Rd.
Bethesda, MD 20816

Molecular Diagnostic Systems, Inc.
3100 Wyman Park Dr.
Baltimore, MD 21211

Molecular Toxicology
335 Paint Branch Rd.
College Park, MD 20742

Nordisk-U.S.A.
3202 Monroe St., Suite 100
Rockville, MD 20852

Oncor, Inc.
209 Perry Parkway, Suite 7
Gaithersburg, MD 20877

Pharma-Tech Research Corp.
6807 York Rd.
Baltimore, MD 21212

P & S Biochemicals, Inc.
7879 Cessna Ave.
Gaithersburg, MD 20879

Survival Technology, Inc.
8101 Glenbrook Rd.
Bethesda, MD 20814

Synax, Inc.
One Kendall Sq., Bldg. 700
Cambridge, MA 02139

University Micro Reference Lab
611P Hammonds Ferry Rd.
Linthicum, MD 21090

Westinghouse Bioanalytic Systems
2096 Gaither Rd.
Rockville, MD 20850

Whittaker M.A. Bioproducts, Inc.
Biggs Ford Rd.
Walkersville, MD 21793

Massachusetts

A/G Technology Corp.
34 Wexford St.
Needham, MA 02194

Advanced Magnetics, Inc.
45 Spenelli Pl.
Cambridge, MA 02138

Amicon Corp.
24 Terry Hill Dr.
Danvers, MA 01923

Angenics
100 Inman St.
Cambridge, MA 02139

Applied Biotechnology
80 Rogers St.
Cambridge, MA 02142

Applied Protein Technologies, Inc.
103 Brookline St.
Cambridge, MA 02139

Bioassay Systems Corp.
225 Wildwood Ave.
Woburn, MA 01801

Biogen
14 Cambridge Center
Cambridge, MA 12142

Biomedical Technologies
378 Page St.
Stoughton, MA 02072

BioPURE
136 Harrison Ave.
Boston, MA 02111

Biotechnica International
85 Bolton St.
Cambridge, MA 02140

Biotechnology Development Corp.
44 Mechanic St.
Newton, MA 02164

Cambridge Bioscience Corp.
35 South St.
Hopkinton, MA 01748

Cambridge Medical Diagnostics
575 Middlesex Turnpike
Billerica, MA 01865

Cambridge Neuroscience Research
1 Kendall Square, Bldg. 700
Cambridge, MA 01730

Cambridge Research Laboratory
195 Albany St.
Cambridge, MA 02139

Charles River Biotechnology
Services
251 Ballardvale St.
Wilmington, MA 01887

Chemgenes
925 Webster St.
Needham, MA 02192

Ciba Corning Diagnostics Corp.
One Kendall Square Bldg., Rm. 200
Cambridge, MA 02139

Collaborative Research, Inc.
2 Oak Park
Bedford, MA 01730

Corning Biomedical Research
1 Kendall Square, Bldg. 200
Cambridge, MA 02139

Creative Biomolecules
35 South St.
Hopkinton, MA 01748

Damon Biotech, Inc.
119 Fourth Ave.
Needham Heights, MA 02194

E. I. du Pont Products
331 Treble Cove Rd.
N. Billerica, MA 01862

Endogen
451 D St., 8th Floor
Boston, MA 02210

The Enzyme Center, Inc.
36 Franklin St.
Malden, MA 02148

Genetics Institute, Inc.
87 Cambridge Park Dr.
Cambridge, MA 02140

Genetics International, Inc.
50 Milk St.
Boston, MA 02109

Genzyme Corp.
75 Kneeland St.
Boston, MA 02111

Hygeia Sciences
330 Nevada St.
Newton, MA 02160

Immunogene, Inc.
124 Mount Auburn St., Suite 200
Cambridge, MA 02138

Immunotech Corp.
P.O. Box 860
Boston, MA 02134

Instrumentation Laboratories
113 Hartwell Ave.
Lexington, MA 02164

Integrated Chemical Sensors
44 Mechanic St.
Newton, MA 02164

Integrated Genetics, Inc.
31 New York Ave.
Framingham, MA 01701

Karyon Technology, Ltd.
333 Providence Highway
Norwood, MA 02062

Milligen
75 Wiggins Ave.
Bedford, MA 01370

Millipore Corp.
80 Ashby Rd.
Bedford, MA 01730

Moleculon Biotech
230 Albany St.
Cambridge, MA 02139

New England Biolabs, Inc.
32 Tozer Rd.
Beverly, MA 0915

Nova Biomedical Corp.
200 Prospect St.
Waltham, MA 02254

Parexel International Corp.
55 Wheeler St.
Cambridge, MA 02138

Penicillin Assays, Inc.
36 Franklin St.
Malden, MA 02148

Repligen Corp.
One Kendall Square, Bldg. 700
Cambridge, MA 02139

Schering Corp.
333 Providence Highway
Norwood, MA 02602

Sepracor, Inc.
33 Locke Dr.
Marlborough, MA 01752

Seragen, Inc.
54 Clayton St.
Boston, MA 02122

Serono Diagnostics, Inc.
100 Longwater Circle
Norwell, MA 02601

Serono Labs
280 Pond St.
Randolph, MA 02368

Swartz Associates
15 Manchester Rd.
Winchester, MA 01890

T-Cell Sciences
840 Memorial Dr.
Cambridge, MA 02139

Toxicon
125 Lenox St.
Norwood, MA 02062

Transformation Research, Inc.
P.O. Box 2411
Framington, MA 01701

Travenol-Genetech Diagnostics
600 Memorial Dr.
Cambridge, MA 02139

Michigan

Covalent Technology Corp.
P.O. Box 1868
Ann Arbor, MI 48106

National Geno Sciences
22150 W. Nine Mile Rd.
Southfield, MI 48034

Neogen Corp.
620 Lesher Pl.
Lansing, MI 48912

Recomtex Corp.
4700 S. Hagadorn, Suite 290
East Lansing, MI 48823

Minnesota

Biotrol, Inc.
11 Peavy Rd.
Chaska, MN 55318

Endotronics, Inc.
8500 Evergreen Blvd.
Coon Rapids, MN 55433

Genesis Labs, Inc.
5182 West 76th St.
Minneapolis, MN 55435

Lifecore, Inc.
315 27th St., S.E.
Minneapolis, MN 55414

Molecular Genetics, Inc.
10320 Bren Road East
Minnetonka, MN 55343

Protatek International, Inc.
1491 Energy Park Dr.
St. Paul, MN 55108

Missouri

Bioclinical Systems, Inc.
5977 S.W. Ave.
St. Louis, MO 63139

Invitron Corp.
4649 Le Bourquet Dr.
St. Louis, MO 63134

Montana

Gametrics, Ltd.
Colony (Wyoming) Route
Alzada, MT 59311

RIBI Immunochem Research, Inc.
P.O. Box 1409
Hamilton, MT 59840

Nebraska

American Laboratories, Inc.
4410 S. 102 St.
Omaha, NE 63127

Biologics Corp.
2720 N. 84th St.
Omaha, NE 68134

New Hampshire

Verax Corp.
HC61 Box 6, Etna Rd.
Lebanon, NH 03766

New Jersey

Agri-Diagnostics Associates
2611 Branch Pike
Cinnaminson, NJ 08077

Alfacell Corp.
225 Belleville Ave.
Bloomfield, NJ 07003

Bio-Recovery, Inc.
P.O. Box 38, 193 Paris Ave.
Northvale, NJ 07647

Bioconsep, Inc.
RD 3, Homestead Rd.
Bldg. 5, Unit 9
Belle Mead, NJ 08502

Biomatrix, Inc.
488 Hobart Rd.
North Brunswick, NJ 08902

Biotest Diagnostics Corp.
6 Daniel Rd., East
Fairfield, NJ 07006

Chemical Dynamics Corp.
P.O. Box 395
South Plainfield, NJ 07080

Cistron Biotechnology, Inc.
10 Bloomfield Ave., Box 2004
Pine Brook, NJ 07058

Clinical Sciences, Inc.
30 Troy Rd.
Whippany, NJ 07981

Cytogen Corp.
201 College Rd., East
Princeton, NJ 08540

DNA Plant Technology Corp.
2611 Branch Pike
Cinnaminson, NJ 08077

Electro-Nucleonics, Inc.
350 Passaic Ave.
Fairfield, NJ 07006

Emtech Research
15 W. Park Dr.
Mount Laurel, NJ 08054

Enzon, Inc.
300-C Corporate Ct.
S. Plainfield, NJ 07080

Glen Mills, Inc.
203 Brookdale St.
Maywood, NJ 07607

Immunomedics, Inc.
5 Bruce St.
Newark, NJ 07103

Inter-Cell Technologies, Inc.
422 Route 206, Suite 143
Somerville, NJ 08876

Interferon Sciences, Inc.
783 Jersey Ave.
New Brunswick, NJ 08901

Liposome Company, Inc.
One Research Way
Princeton, NJ 08540

Marcor Development Corp.
206 Park St.
Hackensack, NJ 07601

Pharmacia Biotechnology Group
800 Centennial Ave.
Piscataway, NJ 08854

Queue Systems, Inc.
P.O. Box 5366
North Branch, NJ 08876

Seapharm, Inc.
791 Alexander Rd.
Princeton, NJ 08540

Unigene Laboratories, Inc.
110 Little Falls Rd.
Fairfield, NJ 07006

New Mexico

Summa Medical Corp.
4272 Balloon Park Rd., N.E.
Albuquerque, NM 87109

New York

An-Con Genetics
1 Huntington Quadrangle
Melville, NY 11747

Applied Microbiology
Brooklyn Navy Yards Bldg. 5
Brooklyn, NY 11205

Bionique Labs, Inc.
Bloomingdale Rd., Route 3
Saranac Lake, NY 12983

Biotechnology General Corp.
375 Park Ave.
New York, NY 10152

Brain Research, Inc.
46 E. 91 St.
New York, NY 10028

Cellular Products
688 Main St.
Buffalo, NY 14202

Charles
688 Main St.
Buffalo, NY 14202

Diagnostic Technology, Inc.
240 Vanderbilt Motor Parkway
Hauppauge, NY 11788

Enzo Biochem, Inc.
325 Hudson St.
New York, NY 10013

Exovir, Inc.
111 Great Neck Rd., Suite 607
Great Neck, NY 11021

Genetic Diagnostics Corp.
160 Community Dr.
Great Neck, NY 11021

Imclone Systems, Inc.
180 Varick St.
New York, NY 10014

Intra Gene International, Inc.
987 Elliott Dr.
Lewiston, NY 14092

Lifecodes Corp.
4 Westchester Plaza
Elmsford, NY 10523

Nuclear and Genetic Technology
172 Brook Ave.
Deer Park, NY 11729

Nygene Corp.
One Odell Plaza
Yonkers, NY 10701

Oncogene Science, Inc.
222 Station Place N., Room 301
Mineola, NY 11501

Praxis Biologics
30 Corporate Woods, Suite 300
Rochester, NY 14623

Sulzer Biotech Systems
230 Crossways Park Dr.
Woodbury, NY 11797

United Biomedical, Inc.
2 Nevada Dr.
Lake Success, NY 11042

North Carolina

Biotherm
P. O. Box 1409
Research Triangle Park, NC 27709

Embrex, Inc.
401 Oberlin Rd.
Raleigh, NC 27605

Environmental Diagnostics, Inc.
P. O. Box 908, 2990 Anthony Rd.
Burlington, NC 27215

Maricultura, Inc.
P.O. Drawer 565
Wrightsville, NC 28480

Mycosearch, Inc.
P.O. Box 941
Chapel Hill, NC 27514

Organon Teknika
800 Capitol Dr.
Durham, NC 27713

Ohio

Agrigenetics Corp.
29400 Lakeland Blvd.
Wickliffe, OH 44092

Enzyme Technology Corp.
783 U.S. 250 E., Route 2
Ashland, OH 44805

North Coast Biotechnology, Inc.
19701 S. Miles Rd.
Warrensville Heights, OH 44128

Ricerca, Inc.
7528 Auburn Rd., Box 100
Painesville, OH 44077

United States Biochemical Corp.
26111 Miles Rd.
Cleveland, OH 44128

Oregon

American Bioclinical
4432 S.E. 16th Ave.
Portland, OR 97202

Antivirals, Inc.
249 S.W. Avery
Corvallis, OR 97333

Bend Research, Incorp.
64550 Research Rd.
Bend, OR 97701

Bentech Laboratories
635 Water Ave. East
Albany, OR 97321

Epitope, Inc.
15425-E Southwest Koll Parkway
Beaverton, OR 97006

Pennsylvania

Biochem Technology, Inc.
66 Great Valley Parkway
Malvern, PA 19355

Biological Energy Corp.
P.O. Box 766, 2650 Eisenhower Ave.
Valley Forge, PA 19482

Bioscience Management, Inc.
BFTC-South Mountain Dr.
Bethlehem, PA 18015

Centocor
244 Great Valley Parkway
Malvern, PA 19355

Cytox Corp.
954 Marcon Blvd.
Allentown, PA 18103

Du Pont Biosystems
368 Turner Way
Aston, PA 19014

Ecogen Inc.
2005 Cabot Blvd. West
Langhorne, PA 19047-1810

Jackson Immunoresearch Lab
872 Baltimore Pike
West Grove, PA 19390

Polybac Corp.
954 Marcon Blvd.
Allentown, PA 18103

Rhode Island

Scott Laboratories
771 Main St.
Fiskville, RI 40182

South Carolina

Fluor Daniel
Daniel Bldg.
Greenville, SC 29602-2170

Tennessee

Biotherapeutics, Inc.
357 Riverside Dr.
Franklin, TN 37064

Texas

Bethyl Labs, Inc.
P.O. Box 850
Montgomery, TX 77356

Biotics Research Corp.
4850 Wright Rd., Suite 150
Stafford, TX 77047

Brown and Root, Inc.
P.O. Box 3
Houston, TX 77001

Detox Industries
12919 Dairy Ashford
Sugar Land, TX 77478

Gamma Biologicals, Inc.
3700 Mangum Rd.
Houston, TX 77092

Granada Genetics Corp.
10900 Richmond Ave.
Houston, TX 77242

Houston Biotech
3606 Research Forest Dr.
The Woodlands, TX 77380

Hyclone, Inc.
P.O. Box 3190
Conroe, TX 77305

Immuno Modulators Labs, Inc.
10521 Corporate Dr.
Stafford, TX 77477

Inland Laboratories
P.O. Box 180456
Austin, TX 78718

Kallestad Laboratories
1120 Capital of Texas Highway, So.
Austin, TX 78746

Monoclonetics International, Inc.
18333 Egret Bay Blvd., Suite 270
Houston, TX 77058

O.C.S. Labs
Box 2868
Denton, TX 76202

Utah

Biomaterials International, Inc.
P.O. Box 8852, 420 Chipeta Way
Suite 160
Salt Lake City, UT 84108

Hyclone Laboratories
1725 S. State Highway 8991
Logan, UT 84321

NPI
417 Wakara Way
Salt Lake City, UT 84108

Virginia

Flow Laboratories, Inc.
7655 Old Spring House Rd.
McLean, VA 22102

Glen Resarch Corp.
P.O. Box 1047
487 Carlisle Dr., Suite A
Herndon, VA 22070

Hazelton Biotechnologies
9200 Leesburg Turnpike
Vienna, VA 22180

Interleukin-2
413 N. Washington St.
Alexandria, VA 22313

Meloy Laboratories, Inc.
6715 Electronic Dr.
Springfield, VA 22151

Washington

Bio Techniques Labs., Inc.
15555 N.E. 33rd St., Biotech Rd.
Redmond, WA 98052

Biocontrol Systems
21414 68th Ave., South
Kent, WA 98032

Biomed Research Labs, Inc.
1115 E. Pike St.
Seattle, WA 98122

Cyanotech Corp.
18748 142nd Ave., N.E.
Woodinville, WA 98072

Ecova Corp.
3820 159th Ave., N.E.
Redmond, WA 98052

Genetic Systems Corp.
3005 First Ave.
Seattle, WA 98121

Immunex Corp.
51 University St.
Seattle, WA 98101

IMRE Corp.
130 5th Ave., North
Seattle, WA 98109

NEORX Corp.
410 W. Harrison St.
Seattle, WA 98119

Oncogen
3005 First Ave.
Seattle, WA 98121

R & A Plant/Soil, Inc.
24 Pasco Kahlotus Rd.
Pasco, WA 99301

Solomon Park Research Laboratories
12815 N. E. 124th St., Suite I
Kirkland, WA 98034

Zymogenetics, Inc.
2121 N. 35th St.
Seattle, WA 98103

West Virginia

Allelic Biosystems
Rt. 1, Box 230
Kearneysville, WV 25430

Wisconsin

Agracetus
8520 University Ave.
Middleton, WI 53562

Agreco
Route 4
Viroqua, WI 54665

Agrigenetics Advanced Science Co.
5649 East Buckeye Rd.
Madison, WI 53716

American Breeders Service
P.O. Box 459, Route 1
DeForest, WI 53532

American Genetics Inc.
7685 Mineral Point Rd.
Verona, WI 53593

Anaquest
2005 W. Beltline Highway
Madison, WI 53718

Bio-Technical Resources, Inc.
1035 S. 7th St.
Manitowoc, WI 54220

Epicenter
2131 Kendall Ave.
Madison, WI 53705

Genetic Designs, Inc.
5146 Anton Dr.
Madison, WI 53719

Hazelton Biotechnologies Corp.
3301 Kinsman Blvd.
Madison, WI 53704

Incell Corp.
1600 W. Cornell
Milwaukee, WI 53209

Knight Hollow Nursery, Inc.
2433 University Ave.
Madison, WI 53705

Molecular Biology Resources, Inc.
5520 W. Burleigh St.
Milwaukee, WI 53210

Pharmacia P-L Biochemicals Inc.
2202 N. Bartlett Ave.
Milwaukee, WI 53202

Promega Biotech
2800 South Fish Hatchery Rd.
Madison, WI 53711

Universal Bioventures Corp.
6143 North 60th St.
Milwaukee, WI 53218

Appendix B

Major Corporations Investing in Biotechnology

Abbott Laboratories
Abbott Park
N. Chicago, IL 60064

Allied Chemical Corp.
Columbia Rd. & Park Ave.
P.O. Box 2245R
Morristown, NJ 07960

Allied-Signal, Inc.
Columbia Rd. & Park Ave.
P.O. 1021R
Morristown, NJ 07960

American Cyanamid Co.
P.O. Box 400
Princeton, NJ 08540

American Home Products
685 Third Ave.
New York, NY 10017

American Hospital Supply Corp.
One American Plaza
Evanston, IL 60201

Amoco Corp.
P.O. Box 400, MS B-1
Naperville, IL 60566

Ares-Serono Laboratories
280 Pond St.
Randolph, MA 02368

Baxter Travenol Labs, Inc.
One Baxter Parkway
Deerfield, IL 60015

Becton Dickinson & Co.
1 Becton Dr.
Franklin Lake, NJ 07417

Bio-Rad Laboratories
2200 Wright Ave.
Richmond, CA 94804

Boehringer Ingleheim Corp.
90 E. Ridge
P.O. Box 368
Ridgefield, CT 06877
(Overseas Only)

Boehringer-Mannheim Corp.
9115 Hague Rd.
Indianapolis, IN 46250

Bristol-Meyers
100 Forest Ave.
Buffalo, NY 14213

Burroughs Wellcome Co.
3030 Cornwallis Rd.
Research Triangle Park, NC 27709

Campbell Institute for Research & Technology
Campbell Soup Co.
Campbell Rd.
Camden, NJ 08101

CIBA GEIGY Corp.
556 Morris Ave.
Summit, NJ 07901
(Overseas only)

Celanese Research Co.
86 Morris Ave., Box 1000
Summit, NJ 07901

Corning Glassworks
Houghton Park
Corning, NY 14831

Del Monte USA
Agricultural Biotechnology Program
P.O. Box 36
San Leandro, CA 94577

Diamond Shamrock
Biotechnology Research
SDS Biotech Corp.
P.O. Box 348
Painsville, OH 44077

The Dow Chemical Co.
1701 Building
Midland, MI 48674

E. I. du Pont de Nemours Co.
Barley Mill Plaza
Wilmington, DE 19898

Eastman Kodak Co.
Bio-Products Division
Rochester, NY 14650

Ecogen Inc.
2005 Cabot Blvd. West
Langhorne, PA 19047-1810

Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

Exxon
180 Park Ave.
Florham Pk, NJ 07932

FMC Corp.
2000 Market St.
Philadelphia, PA 19103

General Electric
R&D Laboratories, 1 River Rd.
Schenectady, NY 12345

General Foods Corp.
250 North St.
White Plains, NY 10625

Gist-Brocades USA, Inc.
5550 77 Center Rd.
P.O. Box 241068
Charlotte, NC 28224
(Overseas only)

Glaxo Inc.
5 Moore Dr., Box 13398
Research Triangle Park, NC 27709

W. R. Grace & Co.
7379 Route 32
Columbia, MD 21044

Hercules R&D
Hercules Plaza
Wilmington, DE 19894

Hoffman-La Rouche Inc.
340 Kingsland St.
Nutley, NJ 07110

Intl. Mineral & Chemical Corp.
2315 Sanders Rd.
Northbrook, IL 60062

Johnson & Johnson
501 George St.
New Brunswick, NJ 08903

Key Pharmaceuticals
18425 N.W. 2nd Ave.
Box 694307
Miami, FL 33269
(subsidiary of Schering-Plough)

Kimberly-Clarke
1400 Holcomb Bridge Rd.
Roswell, GA 30076

Life Technologies Inc.
8717 Grovemount Circle
Gaithersburg, MD 20877

Litton Bionetics, Inc.
1330 A. Piccard Dr.
Rockville, MD 20850

Lubrizol Enterprises
29400 Lakeland Blvd.
Wickliffe, OH 44092

Merck and Company, Inc.
126 East Lincoln Ave.
Rahway, NJ 07065

Miles Laboratories, Inc.
1127 Myrtle St.
P.O. Box 40
Elkhart, IN 46515

Miller Brewing Co.
3939 W. Highland Blvd.
Milwaukee, WI 53201

Monsanto Agricultural Co.
800 N. Lindbergh Blvd.
St. Louis, MO 63166

Natl. Distillers & Chemical Corp.
11500 Northlake Dr.
P.O. Box 429550
Cincinatti, OH 45249

New England Nuclear Corp.
549 Albany St.
Boston, MA 02118

Norwich Eaton Pharmaceuticals, Inc.
Procter & Gamble Co.
Cincinnati, OH 45201
(subsidiary of Procter & Gamble

Olin Corp.
275 S. Winchester Ave.
New Haven, CT 06511

Ortho Pharmaceutical Corp.
Rt. 202
Raritan, NJ 08869
(division of Johnson & Johnson)

Pennwalt Corp.
P.O. Box 1710
Rochester, NY 14603

Pfizer Inc.
Eastern Point Rd.
Groton, CT 06340

Phillips Petroleum Co.
15C4 Phillips Bldg.
Bartlesville, OK 74004

Pioneer Hi-Bred Intl., Inc.
Plant Breeding Division
Box 85
Johnston, IA 50131-0085

RJR Nabisco, Inc.
1100 Reynolds Blvd.
Winston-Salem, NC 27102

Rohm & Haas Co.
Independence Mall West
Philadelphia, PA 19105

Rorer Group Inc.
500 Virginia Dr.
Ft. Washington, PA 19034

Sandoz, Inc.
59 Route 10
East Hanover, NJ 07936

Schering-Plough Corp.
One Giralda Farms
Madison, NJ 07940-1000

Smith Kline & French Labs.
1500 Spring Garden St.
P.O. Box 7929
Philadelphia, PA 19101
(division of Smith Kline Beckman)

Squibb Corp.
P.O. Box 4000
Princeton, NJ 08543-4000

The Standard Oil Co.
200 Public Square
Cleveland, OH 44115-2375

Syntex Corp.
3401 Hillview Ave.
P.O. Box 10850
Palo Alto, CA 94304

Texaco Research Center
Texaco Inc.
Research & Environmental Studies Div.
P.O. Box 509
Beacon, NY 12508

3M
3M Center Building
220-4NE-01
St. Paul, MN 55144

Universal Foods Corp.
433 East Michigan St.
Milwaukee, WI 53202

The Upjohn Co.
7000 Portage Rd.
Kalamazoo, MI 49001

Weyerhauser Co.
Tacoma, WA 98477

Wyeth Laboratories
P.O. Box 8299
Philadelphia, PA 19101
(division of American
Home Products)

Appendix C
Training and Education Initiatives in Biotechnology

Note: The programs and degrees listed here do not include the more traditional disciplines that contribute to biotechnology, such as genetics, molecular biology, microbiology, and chemical engineering, though most of the universities listed here offer those degrees as well. Listing here does not constitute any endorsement or certification by OTA.

California

*California Polytechnic State University
Biochemical Engineering
San Luis Obispo, CA 93407
Degrees Offered: B.S./M.S.
Year of Initiation: 1986

California State University, Hayward
Certificate Program in Biotechnology
Department of Biological Sciences
Hayward, CA 94542
Degrees Offered: M.S. with certificate in Biotechnology
Year of Initiation: 1986

California State University, Los Angeles
Certificate Program in Biotechnology
Department of Biology
5151 State University Dr.
Los Angeles, CA 90032
Degrees Offered: Graduate Certificate in Biotechnology
Year of Initiation: 1987

San Diego State University
Program for Biotechnology Education and Research
Molecular Biology Institute
San Diego, CA 92182
Degrees Offered: Certificate in Recombinant DNA (1983); Certificate in Protein Engineering (1988); M.A. in Biotechnology and Certificate in Agricultural Biotechnology (pending approval).
Year of Initiation: 1980

San Diego State University
California State University System Program for Biotechnology Education and Research
Molecular Biology Institute
San Diego, CA 92182-0328
Degrees Offered: None
Year of Initiation: 1987

San Francisco State University
Genetic Engineering Certificate
Department of Biology
San Francisco, CA 94132
Degrees Offered: Certificate
Year of Initiation: 1983

University of California, Davis
Biotechnology Program
College of Agriculture and Environmental Science
Davis, CA 95616
Degrees Offered: B.S., M.S., Ph.D. in various disciplines
Year of Initiation: Not Applicable

District of Columbia

Catholic University of America
Center for Advanced Training in Cell and Molecular Biology
Room 103 McCort-Ward Building
Washington, DC 20064
Degrees Offered: None
Year of Initiation: 1982

Florida

*University of Florida
Florida Biotechnology R & D Institute
1 Progress Blvd.
P.O. Box 26
Alachua, FL 32615
Degrees Offered: None
Year of Initiation: 1987

*University of Florida
Interdisciplinary Center for Biotechnology Research
1301 Fifield Hall
Gainesville, Florida 32611
Degrees Offered: None
Year of Initiation: 1987

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*Survey information not provided by program to OTA.

76-582 O - 88 - 10 : QL 3

*University of South Florida
Biotechnology Tracks
Tampa, FL 33620
Degrees Offered: Biotechnology Tracks in Chemical Engineering and Biology; Combined B.S./M.S. in Biotechnology is planned
Year of Initiation: 1985

Georgia

*University of Georgia
Biotechnology Center
Athens, GA 30602
Degrees Offered: None
Year of Initiation: 1982

Illinois

University of Illinois—Urbana/Champaign
Biological Engineering Program and Bioprocess Engineering Research Laboratory
Bioprocess Engineering Laboratory Committee
208 North Romine
Urbana, IL 61801
Degrees Offered: M.S. and Ph.D. in Biological Engineering (planned)
Years of Initiation: Research (1986); Engineering Program (1988)

Iowa

*Iowa State University
Biotechnology Program
Office of Biotechnology
1301 Agronomy
Iowa State University of Science and Technology
Ames, IA 50011
Degrees Offered: none
Year of Initiation: 1984

University of Iowa
Biocatalysis: A Graduate Program in Biotechnology
College of Pharmacy
Iowa City, IA 52242
Degrees Offered: No specific biotechnology degree
Year of Initiation: 1983

University of Iowa
Biochemical Engineering/Biotechnology
Department of Chemical & Materials Engineering
Iowa City, IA 52242
Degrees Offered: M.S., Ph.D. in Chemical and Materials Engineering with emphasis in Biochemistry/Biotechnology
Year of Initiation: 1985

University of Iowa Medical School
Iowa Biotechnology Training Program
Department of Microbiology
Iowa City, IA 52242
Degrees Offered: No specific biotechnology degree
Year of Initiation: 1984

Kentucky

University of Kentucky
Biotechnology Undergraduate Degree
Department of Biochemistry
800 Rose St.
Lexington, KY 40536
Degrees Offered: B.S. in Biosciences/Biotechnology
Year of Initiation: 1987

Maryland

University of Maryland, Baltimore County
Master of Science in Applied Molecular Biology
Applied Molecular Biology
Department of Biological Sciences
Catonsville, MD 21228
Degrees Offered: M.S., 5-year B.S./M.S.
Year of Initiation: 1981

Massachusetts

*Becker Junior College
Biotechnician Program
3 Paxton St.
Leicester, MA 01524
Degrees Offered: A.A.S.
Year of Initiation: 1988

Massachusetts Institute of Technology[a]
Biochemical Engineering
Department of Applied Biological Sciences
MIT Room 20A-207
Cambridge, MA 02139
Degrees Offered: M.S. and Ph.D. in Biochemical Engineering
Year of Initiation: 1955

Massachusetts Institute of Technology
Biotechnology Process Engineering Center
Biotechnology Process Engineering Center
Room 20A-207
Cambridge, MA 02139
Degrees Offered: None
Year of Initiation: 1985

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*Survey information not provided by program to OTA.
[a] The Department of Applied Biological Sciences at the Massachusetts Institute of Technology is being phased out.

*Metropolitan College
Boston University
Biotechnology Program
755 Commonwealth Ave.
Boston, MA 02215
Degrees Offered: A.A.S.
Year of Initiation: 1987

Tufts University
Biotechnology Engineering Center
Pearson Building P-103
Medford, MA 02155
Degrees Offered: B.S./M.S., M.S., Ph.D. in Biochemical/Chemical Engineering; Certificate program in biotechnology processing
Year of Initiation: 1986

Worcester Polytechnic Institute
Biotechnology
Department of Biology and Biotechnology
Worcester, MA 01609
Degrees Offered: B.S. and M.S. in biotechnology
Year of Initiation: 1982

Michigan

Ferris State College
Biotechnology Emphasis, B.S., Applied Biology
Department of Biological Sciences
Big Rapids, MI 49307
Degrees Offered: B.S., Applied Biology
Year of Initiation: 1988

Minnesota

University of Minnesota
Program in Microbial Engineering
Box 196
School of Medicine
420 Delaware St., S.E.
Minneapolis, MN 55455
Degrees Offered: M.S. in Microbial Engineering
Year of Initiation: 1984

University of Minnesota
Institute for Advanced Studies in Biological Process Technology
240 Gortner Laboratory
1479 Gortner Ave.
St. Paul, MN 55108
Degrees Offered: Ph.D. minor in Biological Process Engineering is under development
Year of Initiation: 1985

Montana

Montana State University
Institute for Biological and Chemical Process Analysis
Bozeman, Montana 59717
Degrees Offered: None
Year of Initiation: 1983

Nebraska

Central Community College
Biotechnology Program
P.O. Box 1024
Hastings, NE 68901
Degrees Offered: A.A.S.
Year of Initiation: 1986

New Jersey

*Rutgers University
Biochemical Engineering
Department of Chemical and Biochemical Engineering
P.O. Box 909
Piscataway, NJ 08854
Degrees Offered: B.S., M.S., and Ph.D. in Biochemical Engineering
Year of Initiation: 1970

*Rutgers University
Certificate in Biotechnology
Department of Chemical and Biochemical Engineering
P.O. Box 909
Piscataway, NJ 08855
Degrees Offered: Certificate in Biotechnology
Year of Initiation: 1982

*Rutgers University
Center for Advanced Biotechnology and Medicine
P.O. Box 759
Piscataway, NJ 08854
Degrees Offered: None
Year of Initiation: 1986

Rutgers University
Short Courses in Biotechnology
Cook College
Office of Continuing Professional Education
P.O. Box 231
New Brunswick, NJ 08903
Degrees Offered: None
Year of Initiation: 1984

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*Survey information not provided by program to OTA.

Rutgers University
Biotechnology
Cook College
Department of Biochemistry and Microbiology
Lipman Hall
New Brunswick, NJ 08903
Degrees Offered: B.S. in Biotechnology (pending approval)
Year of Initiation: 1986

New York

Cornell University
Cornell Biotechnology Program
Baker Laboratory
Ithaca, NY 14853
Degrees Offered: None
Year of Initiation: 1983

*Monroe Community College
Biotechnology Program
1000 E. Henrietta Rd.
Rochester, NY 14623
Degrees Offered: A.A.S.
Year of Initiation: 1983

Rochester Institute of Technology
Biotechnology
Department of Biology
One Lomb Memorial Dr.
Rochester, NY 14623
Degrees Offered: B.S. in Biotechnology
Year of Initiation: 1983

*State University of New York, Alfred
Biotechnology Program
Alfred, NY 14802
Degrees Offered: A.A.S.
Year of Initiation: 1986

*State University of New York, Buffalo
Center for Biotechnology
School of Medicine
462 Grieder St.
Buffalo, NY 14215
Degrees Offered: None
Year of Initiation: 1984

State University of New York, Fredonia
Bachelor of Science Major, Recombinant Gene Technology
Department of Biology
Fredonia, NY 14063
Degrees Offered: B.S., Recombinant Gene Technology
Year of Initiation: 1983

State University of New York, Plattsburgh/Miner Institute
In Vitro Cell Biology and Biotechnology
Miner Center
Chazy, NY 12921
Degrees Offered: B.S. and M.A.
Year of Initiation: 1980

State University of New York, Stony Brook
Center for Biotechnology
130 Life Sciences Bldg.
Stony Brook, NY 11794
Degrees Offered: None
Year of Initiation: 1983

North Carolina

*North Carolina State University
Biotechnology Program
Raleigh, NC 27695
Degrees Offered: Ph.D. minor in Biotechnology
Year of Initiation: 1982

Technical College of Alamance
Biotechnology
P.O. Box 623
Haw River, NC 27258
Degrees Offered: A.A.S.
Year of Initiation: 1986

University of North Carolina
Program in Molecular Biology and Biotechnology
Room 402 Swing Bldg.
Chapel Hill, NC 27514
Degrees Offered: None
Year of Initiation: 1981

North Dakota

North Dakota State University
Biotechnology Academic Program
Box 5516
Fargo, ND 58105
Degrees Offered: B.S. in Biotechnology
Year of Initiation: 1986

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*Survey information not provided by program to OTA.

Ohio

Case Western Reserve University
Concentration in Biotechnology and Genetic Engineering
Department of Biology
Cleveland, OH 44106
Degrees Offered: B.A./B.S., M.S., Ph.D.
Year of Initiation: 1984

*Ohio State University
Ohio State Biotechnology Center
Rightmire Hall
1060 Carmack Rd.
Columbus, OH 43210
Degrees Offered: Not yet formulated
Year of Initiation: 1987

Pennsylvania

Cedar Crest College
Genetic Engineering Technology Program
Allentown, PA 18104
Degrees Offered: B.S. major in Genetic Engineering
Year of Initiation: 1983

Lehigh University
Applied Biological Science (M.S.)
Center for Molecular Bioscience & Biotechnology
570 A Whitaker Labs
Bethlehem, PA 18015
Degrees Offered: Ph.D. & M.S. Biochemical Engineering
Year of Initiation: 1987

Pennsylvania State University
Penn State Biotechnology Institute
532 Biotechnology Headquarters Bldg.
University Park, PA 16802
Degrees Offered: None specifically in biotechnology
Year of Initiation: 1985

*University of Pittsburgh
Center for Biotechnology and Bioprocess Engineering
911 William Pitt Union
Pittsburgh, PA 15260
Degrees Offered: None
Year of Initiation: 1987

Tennessee

University of Tennessee
Biotechnology
M303 Walters Life Sciences Bldg.
Knoxville, TN 37996
Degrees Offered: M.S. in Life Sciences - Biotechnology
Year of Initiation: 1985

Texas

Texas A & M University
Agricultural Biotechnology
Department of Biochemistry & Biophysics
College Station, TX 77843
Degrees Offered: None specifically in biotechnology
Year of Initiation: 1984

Utah

Utah State University
Center of Excellence in Biotechnology
Logan, UT 84322-4430
Degrees Offered: None specifically in biotechnology
Year of Initiation: 1987

Virginia

Old Dominion University
Biotechnology
Center for Biotechnology
Norfolk, VA 23508
Degrees Offered: M.S. in Biotechology
Year of Initiation: 1987

Wisconsin

Madision Area Technical College
Biotechnology Laboratory Technician Program
3550 Anderson St.
Madison, WI 53704
Degrees Offered: A.A.S.
Year of Initiation: 1987

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*Survey information not provided by program to OTA.

University of Wisconsin
University of Wisconsin Biotechnology Center
1710 University Ave
Madison, WI 53705
Degrees Offered: None
Year of Initiation: 1984

*University of Wisconsin
University of Wisconsin Bioprocess and Metabolic Engineering Program
Department of Chemical Engineering
Madison, WI 53706
Degrees Offered: None
Year of Initiation: 1987

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*Survey information not provided by program to OTA.

Appendix D

Companies Involved in Biotechnology for Waste Degradation

Company	Materials to Be Degraded	Application
Advanced Biocultures Formulations Orange, CA	Phenols Hydrocarbons Oils Greases Pesticides Tars	Domestic sewage
Advanced Mineral Technologies Golden, CO	Heavy metals	Hazardous waste
American Cyanimid Organic Chemicals Division Wayne, NJ		
American Genetics International Arvado, CO	Toxic waste	
Amicon Corp. Danvers, MA		
Aquifer Remediation Systems Princeton, NJ		
Arco Performance Chemicals, Inc. Philadelphia, PA	Paper and pulp	Waste treatment
Atlantic Research Corp. Alexandria, VA		
ATW Caldweld[a] Santa Fe Springs, CA		Toxic waste
Avasco Wheatridge, CO		
Battelle Memorial Institute Columbus, OH	Chlorinated compounds	Hazardous waste
Bethlehem Steel[a] Bethlehem, PA	Phenols	Waste streams
Biochem Technology, Inc. Malvern, PA		
Bioclean, Inc.[a] Bloomington, MN	PCP	Toxic waste
Bio Huma Netics Chandler, AZ	PCB PCP DDT	

[a] Biological treatment methods have been tested or applied in the field.

Company	Materials to Be Degraded	Application
Bioscience Management Bethlehem, PA	Organics	Soil Groundwater
Biospherics Rockville, MD		Wastewater
Biosystems, Inc.[a] Chester Township, PA	Petroleum products Organic pollutants	Groundwater
Biotechnica International Cambridge, MA	Phenol Coal tars Cyanides Heavy metals	Toxic waste
Biotechnology Unlimited, Inc. Houston, TX	Industrial surfactants Petroleum Pesticides Herbicides Organic solvents Halogenated hydrocarbons PAH	Soils Wastewaters Ponds Lagoons
Biotrol, Inc.[a] Chaska, MN	PCP	Groundwater
Cambridge Analytical Associates, Inc. Cambridge, MA	Chlorinated hydrocarbons Chloroethenes	Wastewater
Cecos International, Inc. Buffalo, NY		Spills Toxic waste
Chem-Clear, Inc. Wayne, PA		
Chemical Waste Management Model City, NY		Toxic waste
Celanese Chemical Co., Inc. Corpus Christi, TX		Anaerobic Wastewater
Cytoculture International, Inc. San Francisco, CA		Wastewater
Detox, Inc. Newport Beach, CA		
Detox Industries Houston, TX	PCB PAH DDT Oil Chlordane	Toxic waste
Dupont Wilmington, DE		
Ecova[a] Redmond, WA	Butyl acrylate Solvents	Soils Toxic waste Spills

[a] Biological treatment methods have been tested or applied in the field.

Company	Materials to Be Degraded	Application
Enzon S. Plainfield, NJ		
Flow Laboratories Orange, CA		Sewage treatment
Fluor Corp. Irvine, CA		
General Electric[a] Schenectady, NY	PCB Phenols	Toxic waste Wastewater
General Environmental Science[a] Beachwood, OH	Phenols Hydrocarbons	Toxic waste Non-toxic waste
Genex Corp. Gaithersburg, MD		Waste treatment
Groundwater Decontamination Systems Waldrick, NJ	Methylene chloride	Groundwater
Groundwater Technology, Inc.[a] Norwood, MA	Petroleum products Hydrocarbons Solvents	Groundwater
Haztech[a] Decatur, GA	Petroleum products	Groundwater Hazardous waste Spills
Homestake Mining Co. Reno, NV	Copper cyanide Free cyanide Thiocyanate	Wastewater
Institute of Gas Technology Chicago, IL		Toxic waste
ITT Rayonier, Inc. Shelton, WA	Pulp and paper	
Interbio Naperville, IL	Hydrocarbons	Soils
International Technologies (IT)[a] Torrance, CA	Nonhalogenated organics	Soil Spills Groundwater
Ionics, Inc. Watertown, MA		
Johnston Associates, Inc. Princeton, NJ		
Keystone Environmental Resources[a] Pittsburgh, PA	Creosote Coal tars	Soil Toxic waste
Lab Systems, Inc. Morton Grove, IL		

[a] Biological treatment methods have been tested or applied in the field.

Company	Materials to Be Degraded	Application
Metropolitan Environmental Celina, OH		Hazardous waste Dewatering sludge Groundwater
Microbio Resources San Diego, CA		
Microbe Masters, Inc. Baton Rouge, LA	Phenolics Hydrocarbons Styrene Trimethylamine Ethylene dichloride PCP Creosote	Wastewater
Microlife Techniques Sarasota, FL	Petroleum products Cutting fluids Toluene Napthalene Benzene Phenol Hexane Octane Isophrenols	Wastewater
Miles Laboratories Elkhart, IN		
Motec Mount Juilet, TN	Wood preservatives	Hazardous waste
MycoSearch Chapel Hill, NC		
Occidental Chemical[a] Grand Island, NY	Chlorinated compounds	Hazardous waste Soils
Oxford Environmental New Orleans, LA		
Polybac, Inc. Allentown, PA		
Remediation Technologies, Inc. Kent, WA		
Rollins Environmental Wilmington, DE		Toxic waste
Sybron Biochemical[a] Birmingham, NJ		Wastewater Groundwater Spills
Syntro Corp. San Diego, CA		

[a] Biological treatment methods have been tested or applied in the field.

Company	Materials to Be Degraded	Application
Vertech Treatment Denver, CO	Pesticides Herbicides Phenols Nitrates Cyanides Benzene Aromatics Nonhalogenated hydrocarbons Coal tars Sulfides	Aqueous organics Sludges Soils
Westinghouse Bio-Analytic Systems Madison, PA		Hazardous waste Groundwater
Zimpro, Inc. Rothschild, WI	Organics Acids Hydrocarbons Leachates Herbicides Pesticides Metals	Wastewater Groundwater

[a] Biological treatment methods have been tested or applied in the field.

SOURCE: Jodi Bakst, Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, Washington, DC, 1987.

Appendix E

List of Working Papers

For this special report, OTA commissioned 6 reports on various topics concerning U.S. investment in biotechnology. The manuscripts of the following contract reports are available in three parts from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA, 22161.

Part I: The Biotechnology Industry in the United States

"Report on the Biotechnology Industry in the United States," The Business Studies Program, North Carolina Biotechnology Center, Research Triangle Park, NC. #PB88143599/AS: $38.95 (paper), $6.95 (microfiche).

Part II: Collaborative Research

"Collaborative Research Relationships in Biotechnology," Trudy S. Solomon, Solomon Associates, Washington, D.C. #PB88144209: $19.95 (paper), $6.95 (microfiche).

Part III: Public and Private Sector Roles in the Funding of Agricultural Research

"Public and Private Sector Roles in the Funding of Agricultural Biotechnology Research," Jack Doyle, Agricultural Resources Project, Environmental Policy Institute, Washington, D.C.

"Public and Private Sector Roles in the Funding of Agricultural Biotechnology Research," Richard A. Herrett and Richard J. Patterson.

#PB88143680/AS: $19.95 (paper), $6.95 (microfiche).

Appendix F

List of Workshops and Participants

Workshop on Public Funding of Biotechnology Research and Training
Sept. 9, 1986

David Blumenthal, *Workshop Chair*
Brigham and Women's Hospital Corporation
Boston, MA

Duane Acker
Agency for International Development
Washington, DC

Saiyed Ahmed
National Oceanic and Atmospheric Administration
Rockville, MD

Pierre Ausloos
National Bureau of Standards
Gaithersburg, MD

Roger Crouch
National Aeronautics and Space Administration
Washington, DC

Mary Ann Danello
Food and Drug Administration
Rockville, MD

George Duda
U.S. Department of Energy
Washington, DC

Doug Getter
Iowa Department of Economic Development
Des Moines, IA

Gary Glenn
Centers of Excellence Corporation
Boston, MA

David Kingsbury
National Science Foundation
Washington, DC

Ruth L. Kirschstein
National Institutes of Health
Bethesda, MD

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U.S. Environmental Protection Agency
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Beltsville, MD

Morris Levin
U.S. Environmental Protection Agency
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Veterans Administration
Washington, DC

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The Thomas Edison Program
Columbus, OH

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Food and Drug Administration
Rockville, MD

Joseph Montemarano
New Jersey Commission on Science and Technology
Trenton, NJ

Robert W. Newburgh
Department of the Navy
Arlington, VA

Sue Tolin
U.S. Department of Agriculture
Washington, DC

Workshop on Collaborative Research Arrangements in Biotechnology
April 23, 1987

David Blumenthal, *Workshop Chair*
Brigham and Women's Hospital Corporation
Boston, MA

Wm. Hugh Bollinger
NPI
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Martin C. Carey
Harvard Medical School
Boston, MA

Michael Crow
Iowa State University
Ames, IA

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Argonne, IL

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Malvern, PA

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Rockville, MD

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University of Chicago
Chicago, IL

Kevin M. Ulmer
SEQLTD
Cohasset, MA

Helen Whiteley
University of Washington
Seattle, WA

Martin Yarmush
Biotechnology Process Engineering Center, MIT
Cambridge, MA

Workshop on Factors Affecting Commercialization and Innovation in the Biotechnology Industry

June 11, 1987

Jerry D. Caulder, *Workshop Chair*
Mycogen Corporation
San Diego, CA

Kathy Behrens
Robertson, Coleman & Stephens
San Francisco, CA

Mary Helen Blakeslee
Longwood, FL

Boyd Burton
Biotrol, Inc.
Chaska, MN

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South San Francisco, CA

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Northbrook, IL

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American Cyanamid Company
Princeton, NJ

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Cambridge, MA

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Raritan, NJ

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Crop Genetics International
Hanover, MD

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Microbio Resources, Inc.
San Diego, CA

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Paine Webber
New York, NY

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Ann Arbor, MI

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Hambrecht and Quist
New York, NY

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Smith Kline & French Laboratories
Philadelphia, PA

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Cetus Corporation
Emeryville, CA

Robert D. Weist
Amgen
Thousand Oaks, CA

Workshop on Funding of Biotechnology Research in Agriculture

July 23, 1987

Michael Crow, *Workshop Chair*
Iowa State University
Ames, IA

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Pioneer Hi-Bred International, Inc.
Johnston, IA

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Calgene
Davis, CA

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Riverside, CA

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Appendix G

Acknowledgments

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Abbott Laboratories

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Food and Drug Administration

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National Academy of Sciences

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Madison Area Technical College

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Hambrecht & Quist

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Massachusetts Biotechnology Center of Excellence

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Appendix H

List of Acronyms and Glossary of Terms

List of Acronyms

AAS	—Associate of Applied Science degree
ABC	—Association of Biotechnology Companies
AID	—Agency for International Development
AIDS	—acquired immune deficiency syndrome
ARS	—Agricultural Research Service
BPEC	—Biotechnology Process Engineering Center (MIT)
BS	—Bachelor of Science degree
BSCC	—Biotechnology Science Coordinating Committee
CAH	—chlorinated aromatic hydrocarbon
CARB	—Center for Advanced Research in Biotechnology (MD)
CCL	—Commodity Control List
CERCLA	—Comprehensive Environmental Response, Compensation and Liability Act
CoCom	—Coordinating Committee on Multilateral Export Controls
CSRS	—Cooperative State Research Service (USDA)
CSU	—Colorado State University
DARPA	—Defense Advanced Research Projects Agency
DBC	—dedicated biotechnology company
DDT	—dichloro diphenyl trichroethane
DNA	—deoxyribonucleic acid
DOC	—Department of Commerce
DoD	—Department of Defense
DOE	—Department of Energy
DRR	—Division of Research Resources (NIH)
DURIP	—Defense University Research Initiative Program
EAA	—Export Administration Act
EAAA	—Export Administration Act Amendments of 1985
EOP	—Executive Office of the President
EPA	—Environmental Protection Agency
EPSCoR	—Experimental Program to Stimulate Competitive Research (NSF)
ERC	—Engineering Research Center (NSF)
ERTA	—Economic Recovery Tax Act of 1981
FDA	—Food and Drug Administration
FFDCA	—Federal Food, Drug and Cosmetics Act
FIFRA	—Federal Insecticide, Fungicide, and Rodenticide Act
FTE	—full-time equivalent
GAO	—General Accounting Office
GE	—General Electric Corporation
HERAC	—Health and Environmental Research Advisory Committee (DOE)
HHMI	—Howard Hughes Medical Institute
HSWA	—Hazardous and Solid Waste Amendments of 1984
IBA	—Industrial Biotechnology Association
IND	—Investigational New Drug
IOM	—Institute of Medicine
IPO	—initial public offering
IRP	—Installation Restoration Program
IRS	—Internal Revenue Service
ISU	—Iowa State University
IT	—International Technologies
ITA	—International Trade Administration
ITC	—Investment Tax Credit
MBI	—Maryland Biotechnology Institute
MCTL	—Militarily Critical Technologies List
MIT	—Massachusetts Institute of Technology
MPBC	—Midwest Plant Biotechnology Consortium
MRO	—medical research organization
MS	—Master of Science degree
NAS	—National Academy of Sciences
NASA	—National Aeronautics and Space Administration
NBF	—new biotechnology firm
NBS	—National Bureau of Standards
NCI	—National Cancer Institute (NIH)
NCRA	—National Cooperative Research Act of 1984
NDA	—New Drug Application
NEI	—National Eye Institute (NIH)
NEPA	—National Environmental Policy Act
NHLBI	—National Heart, Lung and Blood Institute (NIH)
NIA	—National Institute on Aging (NIH)
NIAID	—National Institute of Allergy and Infectious Diseases (NIH)
NIAMS	—National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)
NICHD	—National Institute of Child Health and Human Development (NIH)
NIDDK	—National Institute of Diabetes and Digestive and Kidney Diseases (NIH)
NIDR	—National Institute of Dental Research (NIH)
NIEHS	—National Institute of Environmental Health Sciences (NIH)
NIGMS	—National Institute of General Medical Sciences (NIH)
NIH	—National Institutes of Health

NINCDS —National Institute of Neurological and Communicative Disorders and Stroke (NIH)
NLM —National Library of Medicine (NIH)
NMR —nuclear magnetic resonance spectroscopy
NOAA —National Oceanic and Atmospheric Administration
NPL —National Priority List (EPA sites)
NSF —National Science Foundation
NYU —New York University
OBER —Office of Basic Energy Research (DOE)
OECD —Organization for Economic Co-operation and Development
OHER —Office of Health and Environmental Research (DOE)
ONR —Office of Naval Research (DOD)
OSHA —Occupational Safety and Health Administration
OSTP —Office of Science and Technology Policy (EOP)
OTA —Office of Technology Assessment (U.S. Congress)
PAH —polynuclear aromatic hydrocarbon
PCB —polychlorinated biphenyl
PCP —pentachlorophenal
PHSA —Public Health Service Act
PLA —public licensing application
PMA —Pharmaceutical Manufacturers Association
PPA —Plant Patent Act
PTAA —Patent and Trademark Amendment Act
PTO —Patent and Trademark Organization
PVPA —Plant Variety Protection Act
RAC —Recombinant DNA Advisory Committee (NIH)
RCRA —Resources Conservation and Recovery Act of 1976
RDLP —Research and Development Limited Partnership
RIT —Rochester Institute of Technology
SAES —State Agricultural Experiment Stations
SARA —Superfund Amendments and Reauthorization Act
SBIR —Small Business Innovation Research
SJSU —San Jose State University
SSET —Science, Engineering, and Technology; NSF program
SITE —Superfund Innovative Technology Evaluation
SUNY —State University of New York
SUP —Sustaining University Program
TAC —Technical advisory committee
TCDD —chlorinated dioxin
TCE —trichloroethylene
TPA —tissue-plasminogen activator
TRA —Tax Reform Act of 1986
TSCA —Toxic Substances Control Act of 1976
UCSF —University of California, San Francisco
UI —University of Iowa
USAMRIID—U.S. Army Medical Research Institute of Infectious Diseases
USDA —United States Department of Agriculture
VA —Veteran's Administration

Glossary of Terms

Amino Acid: Any of a group of 20 molecules that are linked together in various combinations to form proteins. Each different protein is made up of a specific sequence of these molecules with the unique sequence coded for by DNA.

Antibody: A protein molecule, also called immunoglobulin, produced by the immune system in response to exposure to a foreign substance. An antibody is characterized by a structure complementary to the foreign substance, the antigen, that provoked its formation and is thus capable of binding specifically to the foreign substance to neutralize it. See *antigen* and *monoclonal antibodies*.

Antigen: A molecule introduced into an organism and recognized as a foreign substance, resulting in the elicitation of an immune response (antibody production, lymphokine production, or both) directed specifically against that molecule. See *antibody* and *monoclonal antibodies*.

B lymphocyte: A specialized white blood cell involved in the immune response of vertebrates that originates in the bone marrow and produces antibody molecules after challenge by an antigen. In hybridoma technology, these cells contribute antibody-producing capability to a hybridoma.

Bioaugmentation: A strategy involved in bioremediation that increases the activity of an organism to break down or metabolize a pollutant. This involves reseeding a waste site with bacteria as they die.

Bioenrichment: A strategy involved in bioremediation that enables an organism to survive and break down or metabolize a pollutant. This involves enhancing the site with nutrients or oxygen required by the micro-organism so they survive and grow.

Biomass: The entire assemblage of living organisms, both animal and vegetable, of a particular region, considered collectively.

Bioprocess engineering: Process that uses complete living cells or their components (e.g., enzymes, chloroplasts) to effect desired physical or chemical changes.

Bioreactor: A vessel used for bioprocessing.

Biosynthesis: Production, by synthesis or degradation, of a chemical by a living organism.

Biotechnology: Commercial techniques that use living organisms, or substances from those organisms, to make or modify a product, and including techniques used for the improvement of the characteristics of economically important plants and animals and for the development of micro-organisms to act on the environment. In this report, biotechnology includes the use of novel biological techniques-specifically, recombinant DNA techniques, cell fusion techniques, especially for the production of monoclonal antibodies, and new bioprocesses for commercial production.

Cell culture: The propogation of cells removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements; also used to refer to any particular individual sample.

Cell fusion: Joining of the membrane of two cells, thus creating a hybrid cell that contains the nuclear material from parent cells. Used in making hybridomas.

Chemostats: Growth chamber that keeps a bacterial culture at a specific volume and rate of growth by continually adding fresh nutrient medium while removing spent culture.

Chromosome: The physical structure within a cell's nucleus, composed of DNA-protein complex, and containing the hereditary material—i.e., genes; in bacteria, the DNA molecule in a single, closed circle (no associated protein) comprising a cell's genome.

Cloning: The process of asexually producing a group of cells (clones), all genetically identical to the original ancestor. In recombinant DNA technology, the process of using a variety of DNA manipulation procedures to produce multiple copies of a single gene or segment of DNA.

Cobalamins: A cobalt-containing complex common to members of the vitamin B_{12} group.

Cometabolism: Process by which a substrate is metabolized by a cell while the cell utilizes another substrate as its energy source. Also called fortuitous degradation.

Congeners: A family of related materials.

Cytoplasm: Cellular material that is within the cell membrane and surrounds the nucleus.

Dicot (dicotyledon): Plant with two first embryonic leaves and nonparallel veined mature leaves. Examples are soybean and most flowering plants.

DNA (deoxyribonucleic acid): The molecule that is the repository of genetic information in all organisms (with the exception of a small number of viruses in which the hereditary material is ribonucleic acid—RNA). The information coded by DNA determines the structure and function of an organism.

Enzyme: A protein that acts as a catalyst, speeding the rate at which a biochemical reaction proceeds, but not altering its direction or nature.

Eukaryote(ic): Cell or organism with membrane-bound, structurally discrete nucleus, and other well-developed subcellular compartments. Eukaryotes include all organisms except viruses, bacteria, and blue-green algae. See *prokaryote*.

Fermentation: An anaerobic process of growing micro-organisms for the production of various chemical or pharmaceutical compounds. Microbes are normally incubated under specific conditions in the presence of nutrients in large tanks called fermentors.

Gene: The fundamental physical and functional unit of heredity; an ordered sequence of nucleotide base pairs that produce a specific product or have an assigned function.

Gene expression: The process by which the blueprint contained in a cell's DNA is converted into a product.

Gene therapy: Insertion of normal DNA directly into cells to correct a genetic defect.

Genome: All the genetic material in the chromosomes of a particular organism: its size is generally given as its total number of base pairs.

Germplasm: The total genetic variability, represented by germ cells or seeds, available to a particular population of organisms.

Hybrid: An offspring of a cross between two genetically unlike individuals.

Hybridoma: A cell produced by fusing a myeloma cell (a type of tumor cell that divides continuously in culture and is "immortal") and a lymphocyte (an antibody-producing cell). The resulting cell grows in culture and produces the specific antibody produced by the parent lymphocyte (a monoclonal antibody).

In vitro: Literally, "in glass." Refers to a process, test, or procedure in which something is measured, observed, or produced outside a living organism after extraction from the organism. See *in vivo*.

In vivo: Literally, "in the living". Refers to a process taking place in a living cell or organism. See *in vitro*.

In vivo genetic transfer: The gene of a useful enzyme from one organism is transfered into a pathway of another organism via natural genetic processes such as transduction, transformation, and conjugation (facilitated by transmissable plasmids or transposons).

Liposomes: A structure with a lipid membrane like that of a cell that can be filled with specific substances and then used as a delivery vehicle to transport those substances to the interior of a target cell by fusion with the cell's own membrane. One of several potential delivery vehicles for use in gene therapy.

Monoclonal antibodies: Identical antibodies that recognize a single, specific antigen and are produced by a clone of specialized cells. Commercial quantities of these molecules are now produced by hybridomas.

Monocot (monocotyledon): Plant with single first embryonic leaves, parallel-veined leaves, and simple stems and roots. Examples are cereal grains such as corn, wheat, rye, barley, and rice.

Mutagenesis: The induction of mutation in the genetic material of an organism; researchers may use physical or chemical means to cause mutations that improve the production of capabilities of organisms.

Myeloma: A malignant tumor of an antibody-producing cell. In hybridoma technology, some of these tumor cells have been adapted to cell culture, and these cells contribute immortality to a hybridoma cell line.

Nitrogen fixation: A biological process (usually associated with plants) whereby certain bacteria convert nitrogen in the air to ammonia, thus forming a nutrient essential for growth.

Nucleic acid hybridization: Matching of either DNA or RNA (depending on the organism) from an unknown organism with DNA or RNA from a known organism. This method is used in tropical disease research for identifying species and strains of organisms.

Nucleotide (base): The unit of nucleic acids. The molecules consist of one of four bases—adenine, guanine, cytosine, or thymine/uracil (DNA/RNA) attached to a phosphate-sugar group. The sugar group is deoxyribose in DNA; in RNA it is ribose.

Prokaryote(ic): An organism (e.g., bacteria, virus, blue-green algae) whose DNA is not enclosed within a nuclear membrane. See *eukaryote*.

Protein: A polypeptide consisting of amino acids. In their biologically active states, proteins function as catalysts in metabolism and as structural elements of cells and tissues.

Protoplast fusion: A means of achieving genetic transfer by joining two protoplasts or joining a protoplast with any of the components of another cell.

Recombinant DNA: A broad range of techniques involving the manipulation of the genetic material of organisms; often used synonymously with genetic engineering; also used to describe a DNA molecule constructed by genetic engineering techniques and composed of DNA from different individuals or species.

Somatic cell genetics: Genetics involving any cell in the body except reproductive cells and their precursors.

Somoclonal variation: Genetic variation produced from the culture of plant cells from a pure breeding strain; the source of the variation is not known.

Tissue culturing: In vitro growth in nutrient medium of cells isolated from tissue.

Transformation: Introduction and assimilation of DNA from one organism into another via uptake of naked DNA.

Vadose: The unsaturated zone of the ground above the permanent water table.

Xenobiotics: Industrial chemicals that have a chemical structure not found in natural compounds, which may resist degradation by micro-organisms.

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